

Minor Tranquillizers – Use and Abuse

Resource Book for the Seminar for Doctors to Help Beat Drugs 2003

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Foreword

By President of the Hong Kong Medical Association

As a representative body of the medical profession and a responsible member of the society, the Hong Kong Medical Association is devoted to encourage people to develop a healthy lifestyle. This year, as the fourth seminar sponsored by the Beat Drug Fund, we looked into benzodiazepines, a topic that is concerned by many doctors.

The amendment of the law on 1 August 1996 has resulted in putting the benzodiazepines under the control of the Dangerous Drugs Ordinance. From then on, a doctor can only supply a benzodiazepine to a patient on a named basis, and is required by the law to keep an accurate record of the dose, the quantity of a benzodiazepine he receives from a supplier and of the dose and quantity of a benzodiazepine he supplies to a patient. He must also record the reason for supplying a benzodiazepine to a patient. Failure to do so is a criminal offence. The punishment can be a fine of up to HK\$450,000 and an imprisonment of up to 3 years. Related to this was the introduction of compulsory drug labelling by the Medical Council of Hong Kong.

Many colleagues felt and still feel aggrieved about the putting of the benzodiazepines under the control of the Dangerous Drugs Ordinance and about the introduction of compulsory drug labelling. Some of them stopped using benzodiazepines all together. Many of them were of the opinion that the whole profession should not be punished by the wrongdoing of a few. After the introduction of these measures, it is my observation that the benzodiazepines have become an under-utilised group of drugs, instead of the previously much abused group of drugs. One of the questions we ask today is how to strike a balance, so that our patients can get the most out of benzodiazepines.

During this seminar, we have invited representatives from the Narcotics Division of the Security Bureau to talk about the present situation of the abuse of benzodiazepines. Members were also invited to share their experience concerning the usage of the drug.

We hope that the seminars would give you more information about the different facets of the situation. We invite the Government to take a second look at the relevant laws, so that more patients may benefit from the use of the benzodiazepines.

Dr. the Hon. Lo Wing Lok

President

Foreword

By Chairman of the Organizing Committee on the Seminar for Doctors to Help Beat Drugs

The use of minor tranquillizers in general, and benzodiazepines in particular, has attracted a lot of discussions and debates in recent years. For the proponents benzodiazepines are safe and effective drugs that can be used to overcome anxiety, relax muscles, promote sleep, and even prevent epileptic fits. For the opponents they are subject to abuse and increased tolerance, and may even lead to withdrawal symptoms, as well as psychological and physical dependence. The latter caused international alarms that prompted the United Nations to hold a Psychotropic Convention, and subsequently legally restricted the medical use of benzodiazepines.

In Hong Kong the benzodiazepines are prescription drugs, and are controlled by both the Dangerous Drugs Ordinance and the Pharmacy and Poisons Ordinance. Meanwhile, medical practitioners in Hong Kong have taken the matter very seriously. For example, in April 1996 the Medical Council of Hong Kong have issued guidelines on the proper prescription of narcotics and benzodiazepines (The Medical Council of Hong Kong, 1996). In 2000 the Hong Kong Medical Association conducted a preliminary survey among our members for comments on the Medical Council's guidelines (Advisory Committee on the Use of Psychoactive Agents, HKMA, 2000). However, the clinical use of benzodiazepines is not free from problems. On the one hand, a tiny minority of medical practitioners were found to ignore these guidelines and indiscriminately prescribe far too many benzodiazepines for their patients. On the other hand, many medical practitioners, or even some pharmacies, may find the administrative side of using the benzodiazepines so tedious and troublesome that they begin to use less in quantity, in kinds, or in strength. Meanwhile, some patients may not be able to get their prescriptions properly filled, others may actually feel reluctant to take them.

It is through these problems that another seminar was organized for members of the Hong Kong Medical Association to discuss in more depth on the legal control and clinical use of benzodiazepine and non-benzodiazepine tranquillizers. We are very grateful for the generous financial support of the Beat Drugs Fund and the staunch support of the Narcotics Division, Security Bureau, Hong Kong SAR Government. Personally I would also like to thank all the supporting staff in the Hong Kong Medical Association who made it possible to organize this seminar and to have this monograph published.

Dr. Chen Char Nie

Chairman, Organizing Committee on the Seminar for Doctors to Help Beat Drugs

References

The Medical Council of Hong Kong Council (1996). *Guidelines on the Proper Prescription and Dispensing of Dangerous Drugs by Registered Medical Practitioners*. Promulgated in April 1996.

Advisory Committee on the Use of Psychoactive Agents, Hong Kong Medical Association (2000). *Report on the Preliminary Survey on the "Guidelines on the Proper Prescription and Dispensing of Dangerous Drugs by Registered Medical Practitioners" and Use of Psychoactive Agents*. The Survey was conducted on 24th February 2000 and reported in September 2000.

Anti-drug Legislation and Abuse Trend of Tranquillizers

Mr. Ting Lup Wong

Assistant Secretary for Security (Narcotics)

Introduction

This presentation comprises two parts: the first part gives an outline of the anti-drug legislation in Hong Kong; the latter part provides a brief overview of the trend of tranquillizers abuse in the past ten years.

Hong Kong's Anti-drug Legislation

The major pieces of anti-drug abuse legislation in Hong Kong are: Dangerous Drugs Ordinance, Control of Chemicals Ordinance; Drug Trafficking (Recovery of Proceeds) Ordinance; and, the Pharmacy and Poisons Ordinance. The Dangerous Drugs Ordinance (or DDO) is the principal piece of legislation that deals with dangerous and controlled drugs. Over 150 types of drugs and substances classified into six categories are controlled under this Ordinance, which is jointly enforced by the Hong Kong Police Force (the Police), the Customs and Excise Department (the Customs) and the Department of Health (D of Health).

Constant reviews of DDO are carried out by the Government to ensure that its provisions and hence our control regime is up to date vis-a-vis the latest drug abuse trend, both locally and internationally. For example, having regard to its rising trend of abuse in Hong Kong, ketamine was put under stringent control of the DDO under the First Schedule in December 2000. In October 2001, GHB and 4-MTA were placed under the First Schedule of the DDO for strict control on the recommendation of the United Nations Commission on Narcotic Drugs, and in view of their high abuse potential.

The Control of Chemicals Ordinance is enforced by the Customs. Under the Ordinance, licensing requirements and controls are placed on 25 chemicals to prevent diversion for illicit manufacture of dangerous drugs. Any person who is found to carry out unauthorised import, export or manufacture, supply or possession of these chemicals may be liable to prosecution. The maximum penalty is 15 years' imprisonment and a fine of HK\$1,000,000.

The provisions of the Drug Trafficking (Recovery of Proceeds) Ordinance give the enforcement agencies the authority to trace, restrain, confiscate and recover from criminals the ill-gotten proceeds they obtained from illicit drug trafficking. Under the Ordinance, it is an offence to launder money or deal with property which is known or believed to represent proceeds of drug trafficking. The Ordinance also imposes a duty to report suspicious transaction involving money laundering. The Police and the Customs jointly operate a Joint Financial Intelligence Unit to facilitate the processing of such reports.

The Pharmacy and Poisons Ordinance controls the medical use of drugs through the licensing of manufacturers, wholesalers, retailers and importers/exporters. It also provides for the registration and testing of pharmaceutical products as well as an up-to-date Poisons List. The Ordinance is enforced by the Pharmacy and Poisons Board and contravention of its provisions may, upon prosecution and conviction, attract penalty up to two years' of imprisonment and a fine of HK\$100,000.

Other related anti-drug abuse legislation includes the Drug Dependent Persons Treatment and Rehabilitation Centre (Licensing) Ordinance and the Places of Public Entertainment Ordinance (Amendment of Schedule 1) Regulation. Under the former, which came into effect on 1 April 2002, a licensing scheme has been introduced for all drug treatment and rehabilitation centres with a view to protecting the well being of those persons who undergo treatment and rehabilitation in these centres. The latter aims to bring dance parties held in unlicensed premises under the ambit of the Places of Public Entertainment Ordinance for licensing control to prevent such events from being misused as venues for drug abuse.

Abuse Trend of Tranquillizers

Statistics over the past ten years compiled by the Central Registry of Drug Abuse on this subject reveal some interesting trends and phenomena. In general, there is a rising trend of abuse in tranquillizers in the past ten years, i.e. from 1992 to 2002, albeit it started at a relatively low base. The total number of reported benzodiazepine abusers increased from 317 in 1992 to 1,040 in the first three quarters of 2002, representing an increase of 228%. Midazolam/Triazolam are the two most commonly abused tranquillizers, with 893 persons reported to have abused them in first three quarter of 2002. They are followed by Diazepam (67) and Estazolam (16).

Drug Abusers Reported to CRDA by Type of Drug from 1992 – 2002 (Jan – Sep) (All ages)

| | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 (Jan-Sep) |
|-------------------------|------|------|------|------|------|-------|------|-------|-------|------|-------------------|
| Benzodiazepines | 317 | 634 | 856 | 724 | 866 | 1,101 | 961 | 1,051 | 1,062 | 977 | 1,040 |
| Chlordiazepoxide | * | 14 | 32 | * | * | – | – | * | * | * | * |
| Diazepam | 9 | 6 | 6 | 6 | * | 29 | 25 | 74 | 99 | 55 | 67 |
| Estazolam | – | – | – | – | – | – | * | * | 16 | 12 | 16 |
| Flunitrazepam | 151 | 350 | 476 | 303 | 293 | 125 | 46 | 61 | 45 | 32 | 15 |
| Midazolam/ Triazolam | 172 | 312 | 409 | 440 | 605 | 977 | 888 | 926 | 908 | 879 | 893 |

Note: * Number of reported abuser is suppressed for confidentiality reasons.

Compared with the “all-ages group”, the “under 21 group” showed only a slight increase in the number of reported cases in 2002, when compared with that of 1992. In 1992, there was a total of 74 persons below 21 reported to have abused benzodiazepines. The number moved up slightly to 78 in the first three quarters of 2002.

Drug Abusers Reported to CRDA by Type of Drug from 1992 – 2002 (Jan – Sep) (Under 21)

| | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 (Jan-Sep) |
|-------------------------|------|------|------|------|------|------|------|------|------|------|----------------|
| Benzodiazepines | 74 | 196 | 351 | 235 | 189 | 112 | 77 | 89 | 135 | 58 | 78 |
| Chlordiazepoxide | * | * | 12 | * | * | – | – | – | * | – | * |
| Diazepam | – | – | * | * | – | 6 | 6 | 44 | 78 | 18 | 34 |
| Estazolam | – | – | – | – | – | – | * | – | 10 | – | * |
| Flunitrazepam | 38 | 156 | 284 | 173 | 139 | 46 | 19 | 18 | 12 | * | * |
| Midazolam/ Triazolam | 33 | 49 | 83 | 72 | 64 | 72 | 50 | 34 | 41 | 28 | 18 |

Note: * Number of reported abuser is suppressed for confidentiality reasons.

It seems to suggest that tranquilizers are mainly abused by grown-ups, rather than by young people. Also, while the absolute number of persons abusing tranquilizers is still relatively low compared with other drugs, the rising trend over the past ten years is worrying and needs to be addressed.

No. of Reported Persons by Reporting Agency and Type of Drug in First Three Quarters of 2002

| | Benzodiazepines No. | Chlordiazepoxide No. | Diazepam No. | Estazolam No. | Flunitrazepam No. | Midazolam/ Triazolam No. |
|---------------------------------------|------------------------|-------------------------|-----------------|------------------|----------------------|--------------------------------|
| Police | 534 | 1 | 16 | 13 | 7 | 471 |
| CSD | 450 | 2 | 7 | 5 | 4 | 429 |
| Methadone Clinics | 462 | – | 5 | 2 | 3 | 452 |
| SWD | 15 | – | 3 | 4 | – | 8 |
| Voluntary Agencies | 333 | – | 40 | – | 6 | 273 |
| Outreaching & other youth services | 60 | – | 31 | – | 2 | 12 |
| Hospitals & Clinics | 112 | – | 13 | 3 | 3 | 86 |
| Total | 1,040 | 2 | 67 | 16 | 15 | 893 |

No. of Reported Persons by Reporting Agency and Type of Drug in First Three Quarters of 2002

| | Benzodiazepines | | Chlordiazepoxide | | Diazepam | | Estazolam | | Flunitrazepam | | Midazolam/Triazolam | |
|------------------------------------|-----------------|------|------------------|------|----------|------|-----------|------|---------------|------|---------------------|------|
| | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank | % | Rank |
| Police | 51.3 | (1) | 50.0 | (2) | 23.9 | (3) | 81.3 | (1) | 46.7 | (1) | 52.7 | (1) |
| CSD | 43.3 | (3) | 100.0 | (1) | 10.4 | (5) | 31.3 | (2) | 26.7 | (3) | 48.0 | (3) |
| Methodone Clinics | 44.4 | (2) | - | | 7.5 | (6) | 12.5 | (5) | 20.0 | (4) | 50.6 | (2) |
| SWD | 1.4 | (7) | - | | 4.5 | (7) | 25.0 | (3) | - | | 0.9 | (7) |
| Voluntary Agencies | 32.0 | (4) | - | | 59.7 | (1) | - | | 40.0 | (2) | 30.6 | (4) |
| Outreaching & other youth services | 5.8 | (6) | - | | 46.3 | (2) | - | | 13.3 | (5) | 1.3 | (6) |
| Hospitals & Clinics | 10.8 | (5) | - | | 19.4 | (4) | 18.8 | (4) | 20.0 | (4) | 9.6 | (5) |
| Total | 100.0 | | 100.0 | | 100.0 | | 100.0 | | 100.0 | | 100.0 | |

On reporting of abuse cases, the bulk of the reports were made by the law enforcement agencies, followed by the methadone clinics and voluntary agencies. The reports made by methadone clinics reveal that quite a number of their patients are poly-drug abusers. The relatively small number of reports by the voluntary agencies including out-reaching teams, in fact, dovetailed with the previous observation that the majority of tranquillizer abusers are adults. In comparison, fewer cases had been reported by the hospitals and clinics. Lastly, it is observed no report had been made by medical professionals in private practice.

Regulations on Minor Tranquillizers: Local & Overseas

Prof. Chen Char-Nie

Chairman, Organizing Committee on the Seminar for Doctors to Help Beat Drugs

Introduction

Minor tranquillizers are anti-anxiety drugs, and the majority of anti-anxiety drugs in current use are benzodiazepines. When benzodiazepines were first introduced, they were considered as the safest and most effective anti-anxiety drugs that have ever been available (See Trimble, 1984). Besides, many of them are also effective as anti-convulsants, sleep-promoting agents, as well as muscle relaxants. Unfortunately, popularity led to its misuse, and cases of psychological and physical dependence were reported. This prompted the United Nations (UN) to sound out warning by holding the Convention on Psychotropic Substances in 1971, and put minor tranquillizers under the international drug-control system, side by side with the narcotic drugs. In 1988, the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances made further commitment to eliminate or reduce illicit demand for narcotic drugs and psychotropic substances, and laid down details of control on these two categories of substances. By 1995, 105 psychotropic drugs are under the control of the Psychotropic Convention. Since psychotropic substances have now been considered together with narcotic drugs, it may seem natural for them to be seen as substances with the same degree of toxicity and addictiveness. This article is to review the regulations with respect to the control of psychotropic substances locally and internationally.

Control of Psychotropic Substances in Hong Kong

(A) The Dangerous Drugs Ordinance and the Dangerous Drugs Regulations

In Hong Kong, the Dangerous Drugs Ordinance (DDO, Cap. 134) was enacted in 1969 as a response to the UN's Single Convention on Narcotic Drugs in 1961. It also included the Dangerous Drugs Regulations, which was an expansion of Section 51 in the DDO. Revision to the Ordinance was made in 1984 to include psychotropic substances. The DDO is jointly enforced by the Hong Kong Police Force, the Customs and Excise Department, and the Department of Health. The term "dangerous drug" is defined as "any of the drugs or substances specified in Part I of the First Schedule of the DDO".

The Dangerous Drugs Ordinance includes 8 Parts and 6 Schedules:

Part I gives a short title and terms for interpretation. *Part II* stipulates control of import, export, procuring, supply, dealing in or with, manufacture and possession of dangerous drugs. *Part III* describes issue of licenses and certificates, requirements in connection with lawful import and export of dangerous drugs, and dangerous

drugs in transit. *Part IV* implies statutory authority to procure, supply and possess dangerous drugs. *Part V* lists the divans and equipment used for smoking and injecting (etc.) dangerous drugs, as well as premises used for unlawful trafficking in or manufacture of dangerous drug, and (in *Part VA*) seizure, detention and forfeiture of ships. *Part VI* lays down conspiracy to commit offence under the Ordinance, false statements, aiding, etc. offence under corresponding law, joint trial in certain cases and conviction of other offences. *Part VII* states the evidence required and (in *Part VIIA*) ways in dealing with confidentiality of records. Lastly, *Part VIII* keeps the miscellaneous issues.

Within the *First Schedule*, there are 4 Parts. Part I lists all the 139 dangerous drugs, including narcotic drugs and psychotropic substances. Part II lists preparations to which Ordinance applies with modifications. Part III lists dangerous drugs to which Ordinance applies with other modifications. Part IV lists preparations that may be sold by retail by listed sellers of poisons under Pharmacy and Poisons Ordinance (Cap. 138). *Second Schedule* gives 77 prescribed hospitals and institutions, other than hospitals maintained by the Hong Kong Government. *Third Schedule* stipulates other offences of which defendant may be convicted. *Fourth Schedule* lists 32 reporting agencies. *Fifth Schedule* lists narcotic drugs of exceptional quantities. *Sixth Schedule* lists the newly included benzodiazepine substances (and any of which that are contained in any proportion in any preparation, mixture, extract or other substances), namely alprazolam, bromazepam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, medazepam, nitrazepam, oxazolam, and temazepam.

It is expected that all the drugs listed above must be dealt with according to the regulations of the DDO. In Section 22(1), the persons authorized to be in charge of the listed drugs must be:

- (a) a registered medical practitioner;
- (b) a registered dentist;
- (c) an approved veterinary surgeon;
- (d) the chief pharmacist;
- (e) an authorized person in hospital, health centre or clinic;
- (f) a sister in charge of a ward; and
- (g) a person in charge of a laboratory.

In Section 23(4), “every dangerous drug...shall...be kept in a locked receptacle which can be opened only by him or by some other person authorized”. In paragraph 23(5), “all dangerous drugs...shall be examined at least *once in every month* by a person appointed (*for*) (a) drugs in possession; (b) proper quantity that is not in possession; and (c) supplied to or by or dispensed”.

The Dangerous Drugs Regulations (DDR, Cap. 134, sub.leg.A) further expand the Section 51 of Part VIII of the DDO (Cap. 134). Within the DDR, *Regulations 1 and 2* dealt with citation and interpretation.

Regulation 3 stipulates requirements with respect to prescriptions as follows:

The prescriptions shall:

- (a) be in writing, and signed by the person giving it with his usual signature, and be dated by him;
- (b) be in ink or otherwise so as to be indelible;
- (c) specify the address of the doctor;
- (d) specify the name and address of the patient;
- (e) related to a dentist or veterinary surgeon; and
- (f) &(g) for recognised or unrecognised preparations, specify the total amount of each preparation to be supplied, or drugs packed in ampoules to be injected.

Regulation 4 deals with marking of packages and bottles, as well as their lawful supply by a registered medical practitioner.

Regulation 5 deals with keeping of register or other records. The following provisions must be complied:

- (a) to keep a register and enter therein in chronological sequence in the form specified in the First Schedule true particulars with respects to every quantity of a dangerous drug, obtained by him and with respect to every quantity of a dangerous drug, supplied by him, whether to persons within or outside Hong Kong.
- (b) to use a separate register or separate part of the register for entries made with respect to each of the dangerous drugs specified in paragraph 1 of Part I of the First Schedule to the Ordinance.

The register must be kept on the premises at all times ready for inspection.

Regulation 6 stipulates the requirements for the register. The following requirements must be complied with:

- (a) the class of dangerous drugs to which the entries on any page of any such register relate shall be specified at the head of that page;
- (b) every entry required to be made under Regulation 5 in such register shall be made on the day on which the dangerous drug is received or, as the case may be, on which the transaction with respect to the supply of the dangerous drug by the person required to make the entry takes place, or, if that is not reasonably practicable, on the next day following the said day.
- (c) no cancellation, obliteration or alteration of any such entry shall be made, and every correction of such an entry shall be made only by way of a marginal note or footnote which shall specify the date on which the correction is made;

- (d) every entry required to be made under Regulation 5 in such register, and every correction of such an entry, shall be made in ink or otherwise so as to be indelible;
- (e) such a register shall not be used for any purpose other than the purpose of the Ordinance;
- (f) such person shall if so required by the Director or any public officer authorized in writing by the Director in that behalf – (i) furnish such particulars as may be required with respect to obtaining or supplying by him of any dangerous drug, or with respect to any stock of dangerous drugs in his possession; (ii) for the purpose of confirming any such particulars, produce any stock of dangerous drugs in his possession; and (iii) produce such register and such other books or documents in his possession relating to any dealings in dangerous drugs as may be required.
- (g) a separate register shall be kept in respect of each set of premises at which the person required to keep the register carries on business, but save as aforesaid not more than one register shall be kept at one time in respect of each class of dangerous drug in respect of which he is required to keep a separate register or part of a register, so, however, that a separate register may, with the approval of the Director, be kept in respect of each department of the business carried on by him;
- (h) every such register shall be kept at the premises to which it relates and so as to be at all times available for inspection.

Regulation 7 relates to the preservation of documents. The register, book or other record alike, or any other document, should be kept for a period of two years from the date on which the last entry therein is made.

Regulation 8 relates to the validity of licence under section 18 and fee therefor.

(B) The Pharmacy and Poisons Ordinance and the Pharmacy and Poisons Regulations

The Pharmacy and Poisons Ordinance of 1975 (PPO, Cap. 138) is provided for the control of the medical use of drugs. This Ordinance is mainly concerned with legitimate sales of prescription drugs, and is therefore more concerned with registered pharmacists and manufacturers. It provides for the registration and licensing of manufacturers and the testing of products, as well as drugs under its Poisons List that are only obtainable through lawful prescription by registered medical doctors. It is enforced by the Pharmacy and Poisons Board through the Department of Health of the Government of the Hong Kong SAR. The Pharmacy and Poisons Regulations (PPR) is an expansion of Section 29 of the PPO (Cap. 138), and is a subsidiary part of the PPO. It lays down details of regulations for the control of substances under the PPO.

The PPR has 10 Parts and 9 Schedules. *Part I* lays down the citation, interpretation, and basic restrictions and exemptions. *Part II* gives additional restrictions on the sale of poisons. *Part III* gives supplementary provisions with respect to labelling and containers. *Part IV* defines storage and transport. *Part V* defines special provisions with respect to institutions. *Part VA* lists the sellers of poisons. *Part VB* defines registration of premises. *Part VI* defines wholesale dealers. *Part VII* defines manufacturers. *Part VIII* defines registration of pharmaceutical products and substances. *Part IX* defines sales of medicines. *Part X* includes all miscellaneous issues such as period of record-keeping, penalties, certificates, etc.

Among the 9 Schedules in the PPR, *The First Schedule* is the most important one as it includes virtually every drug or substance that is obtainable on legal prescription. This is therefore the “Poisons List” to which special restrictions apply under Regulations 3 and 5 of the PPO. The list is therefore different from the list of “psychotropic substances” as defined in the UN’s Conventions as it does not include psychotropic substances such as heroin, cannabis, lysergide, amphetamine, etc. However, it includes drugs prescribed in psychiatry, e.g. antidepressants, antipsychotics, lithium carbonates, etc., which however are included neither in the UN’s Psychotropic Convention nor in the First Schedule of the DDO. Nevertheless, the list does include other psychotropic substances such as benzodiazepines. *The Second and Sixth Schedules* list articles or poisons exempted under Regulations 8 or 4 of the PPO. *The Third and Fourth Schedules* list substances or poisons stipulated respectively in Regulation 9 and 14(a). *The Fifth Schedule* defines indication of statement or labels prescribed by Regulation 15 of the PPO. *The Seventh Schedule* lists poisons required under Regulation 21 of the PPO. *The Eighth and Ninth Schedules* are about forms and fees.

Two other ordinances in Hong Kong concerned with drug abuse are the Control of Chemicals Ordinance (Cap. 148) and the Drug Trafficking (Recovery of Proceeds) Ordinance (Cap. 405). Since medical doctors are less involved in these, they are not discussed here.

In summary, psychotropic drugs as defined in the UN’s Psychotropic Convention are controlled by two Ordinances in Hong Kong. The DDO covers both the narcotics and minor tranquillizers, and the PPO deals mainly with prescription medicines including minor tranquillizers. However, within the DDO, minor tranquillizers such as benzodiazepines are controlled by law in the same way, and to the same degree of severity and addictiveness, as narcotic drugs.

The United Nation's Conventions

As stated previously, the Single Convention on Narcotic Drugs in 1961 did not contain minor tranquillizers. And the United Nations' Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances in 1988 formulated actions in accordance with the recommendation of both the 1961 and 1971 Conventions.

The 1971 UN's Convention on Psychotropic Substances

It has listed under the international control for all central nervous system (CNS) stimulants, minor tranquillizers, hypnotics and hallucinogens. There are 4 Schedules with different degrees of addictiveness and control.

Schedule I includes substances that are highly addictive but have little medical use, and are therefore under very strict control. They can only be used by authorized individuals mainly for research purpose. These include hallucinogens such as lysergic acid diethylamide (LSD).

Schedule II includes substances that are highly addictive but have limited medical use, and are therefore also under strict control. But there is no control on authorized individual use. They include CNS stimulants such as amphetamines (occasionally used in narcolepsy, obesity, attention deficit hyperactivity syndrome, etc.), and non-barbiturate non-benzodiazepine hypnotics (methaqualone).

Schedule III includes fast and medium-acting barbiturates that can be abused but are therapeutically useful, including benzodiazepine tranquillizers (flunitrazepam), as well as non-barbiturate non-benzodiazepine hypnotics (glutethimide). Although some of these may still be available on medical prescriptions, proper labelling, packaging and regulated advertising are however required.

Schedule IV includes most benzodiazepine tranquillizers (e.g. diazepam, alprazolam, etc.), tranquillizers (meprobamate), and non-barbiturate and non-benzodiazepine hypnotics (ethchlorvynol) that are liable to abuse but therapeutically useful. Their clinical use is the same as those in Schedule III.

In summary, the United Nations clearly differentiate the controlled substances in terms of their clinical use, degrees of addictiveness and of dangerousness. Minor tranquillizers and non-barbiturate hypnotics are mostly listed in Schedule IV, which is considered as of high level of clinical use, and low level of addictiveness and dangerousness. Its need for legal control is therefore of the lower level. The exception is methaqualone that is listed in Schedule II, and glutethimide and flunitrazepam that are listed in Schedule III.

Control of Psychotropic Substances in the United Kingdom

In the United Kingdom, the Misuse of Drugs Act 1971 provides legal foundation for the control of different kinds of drugs according to their degrees of harmfulness (Ghodsé, 1989). The Misuse of Drugs Regulations 1985 authorizes different classes of individuals who can possess or supply controlled substances in specified situations. It is noteworthy that they use the term “misuse” instead of “abuse”, indicating a mistaken way of drug use that carries less stigmatization than abnormal (indulging) way of drug use.

The Misuse of Drugs Act 1971

The Misuse of Drugs Act 1971 lists 3 classes of substances according to a decreasing order of harmfulness and penalties, and to these drugs doctors are free to prescribe according to their sound medical practice:

- (1) *Class A* includes all major narcotic analgesics (heroin, opium, cocaine, methadone, and pethidine), hallucinogens (LSD, phencyclidine, etc.), and the injectable forms of Class B drugs.
- (2) *Class B* includes other narcotic analgesics (codeine and pholcodine), CNS stimulants (amphetamines and phenmetrazine), hallucinogens (pentazocine), non-benzodiazepine tranquillizers (glutethimide and methaqualone), as well as cannabis and cannabis resin.
- (3) *Class C* includes other CNS stimulants (phentermine, diethylpropion, and mazindol), non-benzodiazepine tranquillizers (meprobamate and methylprylone), non-benzodiazepine and non-barbiturate hypnotics (ethchlorvynol), and benzodiazepine tranquillizers (diazepam, lorazepam, chlordiazepoxide, etc.)

The Misuse of Drugs Regulations 1985

The Misuse of Drugs Regulations 1985 classifies drugs into 4 Schedules, which stipulates regulations in all aspects of practical use by medical doctors:

- (1) *Schedule I* includes substances that have no therapeutic use, and special authorization is required from the Home Secretary for its use mainly in research. These include LSD, cannabis, raw opium, and coca leaf, etc.
- (2) *Schedule II* includes substances that may be useful in medicine but have high dependence liability. There is a need for safe custody of these substances, which should be kept in locked safes, cabinets or rooms according to precise specifications. A register is also required to record the use of these substances. Prescription must be hand-written and signed with date, name and address of the patient, name and address of the prescriber, the drug, strength and form to be dispensed, the dose, and the total quantity or number of dose units to be

dispensed. Repeat and emergency prescriptions at the patient's request are not allowed except prior arrangement, e.g. special treatment for drug addicts. These substances include heroin, morphine, pethidine, methadone, cocaine, amphetamine, etc.

- (3) *Schedule III* includes substances that may be misused and lead to dependence. Legal requirements for prescriptions are the same as those for Schedule II substances, except that *there is no requirements for safe custody (except for diethylpropion) and no need to keep a register*. These substances include barbiturates, diethylpropion, mazindol, phentermine, meprobamate, glutethimide, methyprylone, pentazocine, etc.
- (4) *Schedule IV* includes substances that, although they are prescription-only medicine, they are subject only to minimal control. Therefore, *their prescriptions do not need to follow the legal restrictions imposed for substances listed in Schedules II and III, and there is no need for any safe custody requirements*. These substances include all benzodiazepinen tranquillizers and non-benzodiazepine tranquillizers as well as new hypnotics such as zolpidem.
- (5) *Schedule V* includes drugs that are listed in Schedule II or III, but their amount is so small in quantity that is considered to be harmless. These substances are free from all legal control except that of retaining an invoice for 2 years. They include substances such as Lomotil, in which it contains diphenoxylate (a Schedule II drug) only 2.5 mg, together with atropine sulphate 25 µg.

In summary, the laws in the United Kingdom consider minor tranquillizers as the least harmful among all the misused substances. The non-benzodiazepine tranquillizers such as meprobamate and glutethimide are listed in Schedule III, but all benzodiazepines are listed in Schedule IV. There is no need for safe custody and for keeping a register for drugs listed in Schedules III and IV. But drugs listed in Schedule III must comply with legal requirements for prescriptions. Drugs in these Schedules are of course prescription-only medicines.

Control of Psychotropic Substances in the United States

In the United States, the control of drugs is the responsibility of the Drug Enforcement Agency (DEA, 2003). They classify drugs into 5 Schedules according to their degrees of dependence liability, abuse potentiality and medical use.

- (1) *Schedule I* includes drugs that are unsafe, high potentiality for abuse, and have no medical use. They are expected to be under the strictest control. These include LSD, 3,4-methylenedioxy-methamphetamine (MDMA), marijuana, dimethyltryptamine (DMT), peyote, psilocybin, mescaline, heroin, and a non-benzodiazepine and non-barbiturate hypnotics (methaqualone).

- (2) *Schedule II* includes drugs that may lead to severe psychological or physical dependence, high potentiality for abuse, but have acceptable therapeutic use. They are expected to be under the strict control. These include cocaine, morphine, hydrocodone, amphetamines, phencyclidine, opium, and a non-benzodiazepine and non-barbiturate hypnotics (glutethimide).
- (3) *Schedule III* includes drugs that have a lower potential for abuse than those in Schedules I and II, moderate or low physical dependence, high psychological dependence, moderate potentiality for abuse, but have acceptable therapeutic use. These include benzphetamine, marinol (synthetic THC), anabolic steroid, barbiturates, methyprylone, ketamine, lysergic acid (LSA), dronabinol, nalorphine, etc., as well as a benzodiazepine tranquillizer (Rohypnol or flunitrazepam).
- (4) *Schedule IV* includes drugs that have limited dependence liability, low potentiality of abuse, but have clear therapeutic use. These include benzodiazepines (diazepam, lorazepam, and clonazepam), and non-benzodiazepine tranquillizers (meprobamate), as well as others (fenfluramine, cathine, diethylpropion, mazindol, pentazocine, etc.).
- (5) *Schedule V* includes drugs that have low potential for abuse, limited physical or psychological dependence, but have acceptable therapeutic use. These include buprenorphine, codeine (less than 200 mg%), dihydrocodeine (less than 100 mg%), pyrovalerone, etc.

In summary, benzodiazepines are seen by the Americans as of limited liability for dependence and of low potential for abuse. They are therefore listed in Schedule IV and are very different from, and much less harmful than, the narcotics, CNS stimulants and hallucinogens as listed in Schedules I, II, and III. The exception is methaqualone that is listed in Schedule I, glutethimide that is listed in Schedule II, and flunitrazepam that is now promoted to Schedule III because of its potential abuse as a “date-rape” substance.

Control of Psychotropic Substances in Canada

The Controlled Drugs Substances Act 1996

In Canada, the Controlled Drugs Substances Act 1996 classifies substances to 8 Schedules according to their degrees of dependence liability, abuse potentiality and medical use. In general, it is similar to the American regulations with some minor differences. The classification is as follows:

- (1) *Schedule I* includes substances that are unsafe, severe level of dependence liability, and no medical use. These include heroin, opium, methadone, cocaine, buprenorphine, mescaline, phencyclidine, fentanyl, tilidine, etc.

- (2) *Schedule II* includes drugs that have severe dependence liability, high potentiality of abuse, but have some therapeutic use. They are expected to be under the strict control. These include cannabis, cannabis resin, etc.
- (3) *Schedule III* includes drugs that have moderate or low dependence liability, moderate potentiality of abuse, but have therapeutic use. These include amphetamines, methaqualone, methylphenidate, flunitrazepam, psilocybin, mescaline, gamma-hydroxybutyrate (GHB), etc.
- (4) *Schedule IV* includes drugs that have limited dependence liability, low potentiality of abuse, but have clear therapeutic use. These include diazepam, alprazolam, chlordiazepoxide, midazolam, lorazepam, glutethimide, barbiturates, cathine, diethylpropion, phenmetrazine, anabolic steroid, etc.
- (5) *Schedule V* is for phenylpropanolamine, pyrovalerone, etc.
- (6) *Schedule VI* is for ephedrine, pseudoephedrine, and LSA.
- (7) *Schedule VII* is for cannabis of 3 Kg in quantity.
- (8) *Schedule VIII* is for cannabis of 30 Kg in quantity.

In summary, Canadians, like their American counterpart, list benzodiazepines and non-benzodiazepine tranquillizers (meprbamate) in Schedule IV except methaqualone and Rohypnol, which are listed in Schedule III. Both the benzodiazepine and non-benzodiazepine tranquillizers are therefore considered as of limited liability for physical dependence and of relatively low potential for abuse.

Control of Psychotropic Substances in the European Economic Countries

In some European countries, e.g. Spain, Ireland, Italy, the Netherlands, Portugal, Luxembourg, and the United Kingdom, the penalty for a drug offence varies according to the nature of the substance involved. In the remaining European countries, the law officially does not recognise differences between drugs, and drug offences may incur the same penalty regardless of the substances involved (ELDD, 2003).

- (1) **Spain:** Spanish legislation places under control narcotic drugs and psychotropic substances in accordance with the UN Conventions.
- (2) **Ireland:** There are 5 Schedules for drug control. *Schedule I* refers to cannabis, LSD, mescaline, opium, etc.; *Schedule II* refers to cocaine, heroin, methadone, morphine, etc.; *Schedule III* refers to other psychotropic substances; *Schedule IV* refers to medicaments; and *Schedule V* refers to specific preparations.
- (3) **Italy:** There are 6 Schedules. *Schedule I* refers to opium, cocaine, hallucinogens, some amphetamines; *Schedule II* refers to cannabis; *Schedule III* refers to barbiturates; *Schedule IV* refers to medical substances; *Schedule V* refers to preparations of substances mentioned in Schedules I to III; and *Schedule VI* refers to antidepressants, stimulants, etc.

- (4) **The Netherlands:** There are 2 Schedules. *Schedule I* includes substances with unacceptable risks: *Ia* refers to opiates, coca derivatives, cannabis; *Ib* refers to codeine; and *Ic-d* refers to psychotropic substances. *Schedule II* includes other substances: *Ila* refers to tranquillizers; and *Iib* refers to cannabis.
- (5) **Portugal:** There are 6 Schedules. *Schedule I* includes *Ia* (opiates), *Ib* (coca and derivatives), and *Ic* (cannabis and derivatives). *Schedule II* includes *Ila* (hallucinogens), *Iib* (amphetamines), and *Iic* (barbiturates). *Schedule III* includes specific preparations. *Schedule IV* includes tranquillizers and analgesics. *Schedules V and VI* include precursors.
- (6) **The United Kingdom:** Previously mentioned.
- (7) **Belgium:** There is no formal legal distinction between drug schedules. Substances listed by Royal Decree are: (1) narcotic substances (often referred to as S) that include opium, heroin, cocaine, morphine, methadone, cannabis, etc.; and (2) psychotropic substances (often referred to as P) that include some amphetamines, hallucinogens, MDMA, etc. P is subclassified into Chapters I, II (further subdivided into 1a, 1b, and 2), III, and IV. Minor tranquillizers including benzodiazepines are included in PIII. Buprenorphine, flunitrazepam, pemoline, pentazocine, phendimetrazine, and phentermine are listed in PIII/PIV, whereas phenylpropranolamine and prolintane are listed in PIV.
- (8) **Denmark:** There are 5 Schedules. *Schedule A* refers to cannabis, heroin, prepared opium, etc. *Schedule B* refers to cocaine, MDMA, amphetamines, methadone, etc. *Schedule C* refers to codeine, etc. *Schedule D* refers to barbiturates, etc. *Schedule E* refers to tranquillizers including benzodiazepines.
- (9) **Germany:** There are 3 Schedules. *Schedule I* refers to illicit drugs that include heroin, cannabis, LSD, etc. *Schedule II* refers to licit, but not prescription, drugs. *Schedule III* refers to drugs that are on prescriptions only, e.g. morphine, methadone, barbiturates, cocaine, codeine, tranquillizers, etc.
- (10) **Greece:** There are 4 Schedules. *Schedule I* refers to cannabis, heroin, LSD, and other hallucinogens. *Schedule II* refers to cocaine, methadone, and opium. *Schedule III* refers to amphetamines. *Schedule IV* refers to barbiturates and tranquillizers.
- (11) **France:** There are 4 Schedules. *Schedule I* refers to cannabis, heroin, cocaine, and methadone. *Schedule II* refers to codeine. *Schedule III* refers to hallucinogens, i.e. LSD, mescaline, MDMA, and amphetamines. *Schedule IV* refers to hallucinogenic mushrooms, presumably psilocyn or psilocybin.
- (12) **Austria:** There are 5 Schedules for narcotics, 1 Schedule for psychotropic substances, and 2 Schedules for precursors. *The Schedule on Psychotropic Substances* includes substances listed in *Schedules III* (i.e. barbiturates) and *IV* (i.e. tranquillizers) of the 1971 UN's Convention on Psychotropic Substances.

- (13) **Finland:** There are 4 Schedules for narcotics, 4 Schedules for psychotropic substances, and 2 Schedules for precursors. For psychotropic substances, *Schedule I* includes 2,5-dimethoxyamphetamine (DMA), LSD, and MDMA. *Schedule II* includes amphetamines and THC. *Schedule III* includes barbiturates. *Schedule IV* includes benzodiazepines.
- (14) **Sweden:** There are 4 Schedules. *Schedule I* refers to cannabis, heroin, MDMA, and LSD. *Schedule II* refers to amphetamines, cocaine, methadone, and opium. *Schedule III* refers to codeine. *Schedule IV* refers to barbiturates, benzodiazepines, and barbital.

In summary, European countries list minor tranquilizers including benzodiazepines in the lowest category of their drug schedules. Although it is not clear if this indicates a legally less restrictive attitude, the impression from the United Kingdom would appear to suggest that this is so.

Control of Psychotropic Substances in the People's Republic of China

In China, two documents were issued by the State Council with respect to the control of narcotic drugs and psychotropic substances (Jiang and Wan, 1992). *The Control of Narcotic Drugs* was issued in 1987, which covers 118 substances and is similar in content to the UN Single Convention of 1961. *The Control of Psychotropic Substances* was issued in 1988, in which psychotropic substances are divided into two categories. The first category includes 47 substances, e.g. amphetamines, MDMA, cathinone, methylphenidate, phencyclidine, phenmetrazine, secobarbital, delta-9-THC, buprenorphine, caffeine, etc. The second category includes 119 substances, e.g. barbiturates, benzodiazepines, ethchlorvynol, etilamfetamine, pemoline, methyprylon, phendimetrazine, phentermine, etc.

For the use of narcotic drugs, the legal restrictions are clearly stated in Chapter 6 of the 1987 Control of Narcotic Drugs. First, it must be approved and given the purchase license card. Second, the dosage must not be prescribed for more than 2-3 days at a time, and certainly not more than 7 days continuously. Third, the prescriber must clearly sign the prescription and make record for it. Fourth, the substances must be kept by a specified person in specified locked cabinet with separate record of the amount in and out. The record should be kept for 3 years. For the use of psychotropic substances, the above restrictions are not required. Category I psychotropic substances can only be dispensed in a specially approved unit but not in any outpatient clinic, whereas Category II psychotropic substances are however free of such restriction. The length of each prescription for the former is up to 3 days, and up to 7 days for the latter.

In summary, the legal restriction in China makes a clear difference between the narcotic drugs and psychotropic substances. Even in the latter, minor tranquilizers including benzodiazepines as listed in Category II are different from the Category I substances. They are not required to make a register, to be kept in a locked safe, or to check the number of tablets every month.

Control of Psychotropic Substances in Taiwan

In Taiwan, there are 4 Schedules (Li, 2002). *Schedule I* refers to opium, morphine, heroin, cocaine, dihydroetorphine, etc. *Schedule II* refers to methadone, pentazocine, pethidine, codeine, methaqualone, amphetamines, MDMA, cathinone, paramethoxyamphetamine, cannabis, phencyclidine, psilocybin, mescaline, LSD, etc. *Schedule III* refers to buprenorphine, tramadol, barbiturates, triazolam, flunitrazepam, ketamine, some codeine, etc. *Schedule IV* refers to diazepam, alprazolam, lorazepam, meprobamate, zolpidem, zopiclone, and some codeine, etc. Organic solvents, nitrites and nitrogen monoxide remain unclassified.

For substances listed in Schedules I and II, there is restriction on manufacture, transport, import/export, wholesale, and the amounts purchased are limited. There is a requirement for prescription only, which cannot be repeated. There is also legal requirement for a locked safe or cabinet and for a record of the patient's name and identity card. However, Schedule IV substances do not have such legal requirements. Schedule III substances may have to fulfil some but not all of the above requirements.

In summary, minor tranquillizers including benzodiazepines as listed in Schedule IV, except flunitrazepam and triazolam, are not subjected to the same legal restrictions as substances listed in Schedules I, II, and III.

Discussion

This review is to examine how minor tranquillizers, and benzodiazepines in particular, are treated by the law either locally or overseas. Whereas many Western countries including the United Kingdom, as well as China and Taiwan, have separate schedules of law for narcotic drugs and psychotropic substances including minor tranquillizers, Hong Kong is the only jurisdiction that has just one schedule for all the controlled drugs. This is especially surprising as Hong Kong was related to the United Kingdom in the past, and has since 1997 been a Special Administrative Region of the People's Republic of China. On the other hand, although there is in Hong Kong one drug schedule for all the controlled substances, i.e. dangerous drugs as defined in Hong Kong, irrespective of their illicit and licit use or of different degrees of dangerousness and addictiveness, sentencing guidelines are in practice available with respect to the kind and weight of trafficking substances (Chen, 1999). A more logical or scientific classification of abused substances, or appropriately designed schedules of control substances, may offer better help to our judicial system.

On the clinical side, the one-and-only-one schedule for all controlled drugs has dumped into one basket all drugs with different degrees of dangerousness and addictiveness. This has created confusion among lay people, some of whom have begun to reject proper drug treatments. Under the Dangerous Drugs Ordinance, benzodiazepine drugs are treated similarly with heroin, opium, cocaine, or amphetamines, they are naturally seen as dangerous

and undesirable as any of these substances. Furthermore, under the Pharmacy and Poisons Ordinance, the benzodiazepines are officially listed and labelled as “poisons” (毒品), together with other drugs used in psychiatry as well as those used in other fields of medicine, they give the general public several wrong impressions. First, they are very dangerous prescription drugs. Second, they are as dangerous as the tricyclic antidepressants or lithium (in fact, quite the opposite). Third, they are as dangerous as other drugs used in medicine, e.g. the active principle of supra-renal gland (again, quite the opposite). The general public and patients seeking psychiatric consultations may therefore see that the benzodiazepines are “poisons to be avoided” as much as possible, although they are prescription drugs. Some patients, especially those with higher level of anxiety, may even be reluctant to take other medications in psychiatry lest they may become “addicted” to them.

It is even worse when there is confusion about drug terminology. Psychiatrists have in the past referred to drugs used in psychiatry as “psychotropic drugs”. For example, Kane and Lieberman’s book (1992), *Adverse Effects of Psychotropic Drugs*, in which drugs used in psychiatry were discussed. Unfortunately, the UN’s Convention on Psychotropic Substances in 1971 includes all controlled substances that influence the CNS. The term “psychotropic substances” accordingly applies to hallucinogens, central stimulants, cannabis, barbiturates, buprenorphine, minor tranquilizers, etc., with the exception of alcohol and nicotine. This has created much confusion in the general public, and perhaps among some medical specialists or government officials as well, the term “drugs used in psychiatry” (精神科藥物) has mistakenly become the common term referring to all the “dangerous drugs” or “poisons” under the laws.

It is of course important that medical practitioners should follow the principles of rational prescriptions, i.e. the dose of benzodiazepines is kept at minimum, the duration short, and other alternative treatments (e.g. behaviour, cognitive, supportive psychotherapy, or other antidepressants) considered. But are these drugs so dangerous and so addictive that require them to be treated in the same way as the deadly heroin and cocaine? Should Hong Kong learn from the experiences of other developed countries or jurisdictions in the classification of all the controlled substances or drugs under the law? There are many reasons why such a classification is urgently needed with respect to the clinical use of minor tranquilizers in general and benzodiazepines in particular.

First, the 1971 UN’s Convention on Psychotropic Substances included in its 4 schedules many different categories of psychotropic agents in addition to benzodiazepines or anti-anxiety drugs. *Schedule I* contains hallucinogens such as lysergic acid diethylamide (LSD), which is not used in medicine. *Schedule II* contains CNS stimulant drugs such as amphetamines, which are only occasionally used by neurologists or sleep specialists for narcolepsy patients, and by child psychiatrists or paediatricians for children with attention deficit disorders with or without hyperactivity. Analogues of amphetamines may also be

used by physicians to suppress appetite and to lose weight. *Schedule III* contains barbiturates which are not used any more in the treatment of insomnia, although some (e.g. phenobarbitone) may still be used as anticonvulsants by neurologists and/or paediatricians. *Schedule IV* contains minor tranquillizers and hypnotics, which are indeed used by psychiatrists. But it also contains other analgesics that are used by physicians or pain specialists.

Second, there are many drugs used in psychiatry that are not included in the UN's Convention on Psychotropic Substances. For example, antipsychotic drugs, e.g. benzodiazepines, sulpiride, amisulpride, risperidone, olanzapine, quetiapine, haloperidol, do not produce physical or psychological dependence. Antidepressants, e.g. amitriptyline, imipramine, and doxepin, or atypical antidepressants such as fluoxetine, paroxetine, citalopram, mirtazapine, and venlafaxine, also do not cause physical or psychological dependence. Mood stabilizers such as lithium and some newer anticonvulsants, and so are newer drugs for dementias such as the anticholinesterase inhibitors, are also not addictive drugs.

Third, the benzodiazepines are in fact clinically effective anti-anxiety drugs, and many of them also have anticonvulsant, sleep-promoting, and muscle relaxing effects. The pharmacological mechanisms of all benzodiazepines, like barbiturates and alcohol, are to facilitate the actions of an inhibitory amino acid neurotransmitter, gamma-aminobutyric acid (GABA). The synaptic actions of GABA are mediated by two receptor types, GABA_A and GABA_B receptors. GABA_A receptor, being the predominant receptor type, is composed of multiple subunits, commonly α , β and γ . It has been shown that, by binding to the α subunit at the GABA_A receptor, benzodiazepines facilitate the ability of GABA to bind and activate the subunit. This in turn activates the chloride channel, leading to hyperpolarization (i.e. inhibition) of the nerve cells (Hymen and Nestler, 1993).

Fourth, benzodiazepines are clinically safe drugs to use. According to the Physicians' Desk Reference (1999), the oral lethal dose (LD₅₀) for diazepam is 720 mg/kg in mice and 1,240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey caused death on the sixth day. Yet, clinically it is prescribed in the range of 2-10 mg at a time, or 2-20 mg per day for human beings weighing 50-60 Kg. It is of course important to recognise that benzodiazepines may produce withdrawal symptoms and increase tolerance, leading to psychological and physical dependence. However, its psychological and physical dependence are not as serious and as addictive as that caused by the narcotic drugs such as heroin.

References

- Chen, C.N. (1999). 《英漢藥物濫用與艾滋病詞匯》(*Anglo-Chinese Glossary on Drug Abuse and AIDS*), pp. 385-386. Beijing: Joint Publishing House of the Beijing and Peking Union Medical Universities.
- DEA (2003). DEA Drug Scheduling. <http://www.dea.gov/pubs/scheduling.html/>
- ELDD (2003). Classification of illicit drugs in the EU. European Legal Database on Drug, an EMCDDA Project. <http://eldd.emcdda.org/trends/classification.shtml/>
- Ghodse, H. (1989). The law and drug-control policy. In: *Drugs and Addictive Behaviour. A Guide to Treatment*, 2nd edition, pp. 333-348. Oxford: Blackwell Science.
- Hymen, S.E. and Nestler, E.J. (1993). *The Molecular Foundations of Psychiatry*, pp. 150. Washington, D.C.: American Psychiatric Press.
- Jiang, Zuo-Ning (姜佐寧) and Wan, Wen-Peng (萬文鵬) (1992). 《藥物濫用》(*Drug Abuse*). Beijing: Science Publications.
- Kane, J.M. and Lieberman, J.A. (1992). *Adverse Effects of Psychotropic Drugs*. New York: The Guilford Press.
- Li, Jih-Heng (李志恒) (2002). 《藥物濫用》(*Drug Abuse*). Taipei: National Narcotics Bureau.
- The Government of the Hong Kong Special Administrative Region (1968). *Dangerous Drugs Ordinance (Cap. 134)*. Up to date as of 8 November 2002. Hong Kong: Government Printer.
- The Government of the Hong Kong Special Administrative Region (1968). *Dangerous Drugs Regulations (Cap. 134, sub.leg. A)*. Up to date as of 8 November 2002. Hong Kong: Government Printer.
- The Government of the Hong Kong Special Administrative Region (1975). *Pharmacy and Poisons Ordinance (Cap. 138)*. Up to date as of 8 November 2002. Hong Kong: Government Printer.
- The Government of the Hong Kong Special Administrative Region (1975). *Pharmacy and Poisons Regulations (Cap. 138, sub.leg. A)*. Up to date as of 8 November 2002. Hong Kong: Government Printer.
- Trimble, M. (ed.) (1984). *Benzodiazepines Divided. A Multidisciplinary Review*. Chichester: John Wiley & Sons.

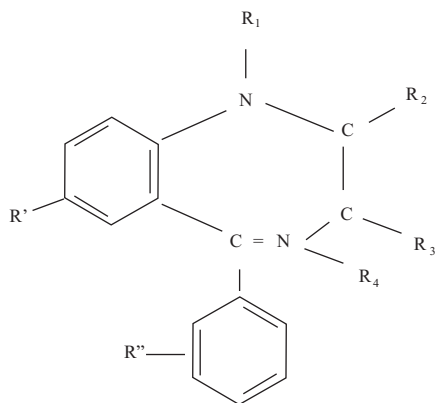
Use and Misuse of Benzodiazepine Sedatives

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Benzodiazepines are a class of medicine developed since 1959 with the basic structure involving 2-aminobenzodiazepine-4-oxidate as in Figure 1. Modification of chemical structures at various positions alters the properties of the benzodiazepine and form different benzodiazepines. Research indicates that this class of medicine increases the activity of the γ -aminobutyric acid (GABA) receptor in the presence of GABA. This in effect decreases cellular excitability through increases in inward movement of chloride ions through the chloride channel. GABA receptors are widely distributed in the nervous system and benzodiazepines do not act on all of these receptors. Some of the actions of benzodiazepine can be understood by the effects of GABA in various parts of the nervous system. Ataxia is related to GABA neurons in the cerebellum, sedation in the reticular formation, memory effects in the hippocampus, and muscle relaxant properties in the spinal cord. It is with the effect of benzodiazepines on the reticular formation that it is used as a sedative.

Figure 1. Molecular Structure of Benzodiazepine Nucleus



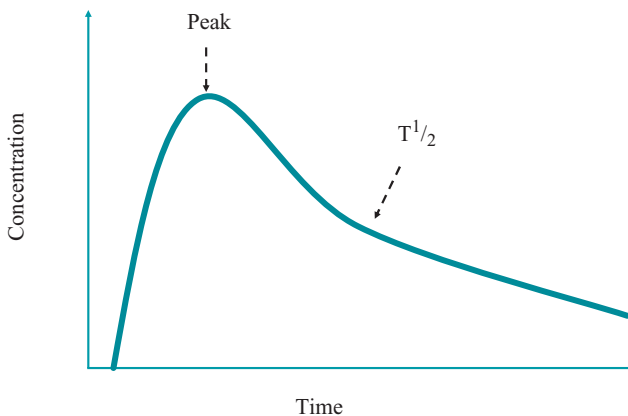
The use of a medicine as a sedative requires the knowledge of how quickly the medicine starts to have effect on a person, and how long the effect of the medicine lasts in a person.

When a medicine is taken by the oral route, it passes down the gastrointestinal tract, gets absorbed, passes the metabolism of the liver, goes into the circulatory system, gets carried to the brain, crosses the blood brain barrier, and gets to the receptor sites for its action. The time of onset of a medicine depends on all these steps. Usually a more lipid soluble medicine gets absorbed more quickly and crosses the blood brain barrier more quickly. A simplified

way to indicate an idea of the time of onset of action of a particular medicine is its time to attain the peak blood level of the medicine after a single oral dose.

After a medicine has reached its peak level at its sites of action, the level of the medicine decreases with re-distribution of the medicine to other parts of the body, and the medicine is also metabolized and gradually excreted from the body. The time for the blood level of the medicine to be reduced by half from its peak blood level is called its half life ($T_{1/2}$) as in Figure 2. This $T_{1/2}$ of a medicine allows a simple way to indicate the duration of action of that medicine.

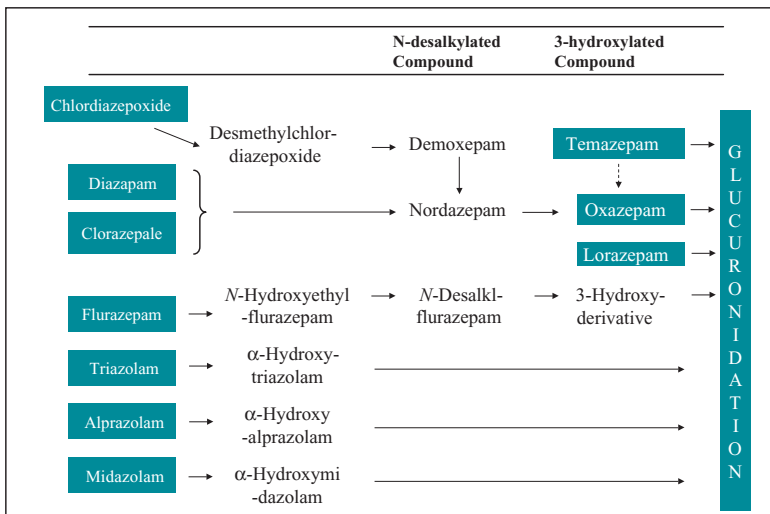
Figure 2. The Blood Concentration of a Medicine after a Single Dose of Medicine



When a medicine is metabolized in the liver, it needs to be noted that some of the metabolites may have active pharmacological effect. The active metabolite has its own $T_{1/2}$ that may be shorter than, as long as, or longer than the $T_{1/2}$ of the original medicine. When a medicine has an active metabolite that has longer $T_{1/2}$ than its original medicine, the duration of action of the original medicine becomes effectively as long as that of the active metabolite.

Table 1 shows the major metabolic relationships between some of the benzodiazepines. Chlordiazepoxide is a medicine with intermediate duration of action with average $T_{1/2}$ in the range between 6 to 20 hours. It is metabolized in steps into active metabolites including desmethyldiazepam, demoxepam, nordiazepam and oxazepam before glucuronidation into an inactive metabolite. While desmethyldiazepam and oxazepam are also of intermediate duration of action, demoxepam and nordiazepam are both of long duration of action with duration longer than twenty hours. Thus in effect chlordiazepoxide becomes a medicine with long duration of action.

Table 1. Major Metabolic Relationships Between Some of the BDZs



Diazepam is itself a medicine of long duration of action. It has active metabolites including nordazepam of long duration of action and oxazepam of intermediate duration of action. Diazepam remains in effect a medicine with long duration of action.

Clorazepate is itself not an active medicine. It is metabolized and absorbed in the stomach. It has an active metabolite nordazepam with long duration of action. In effect clorazepate acts as a medicine with long duration of action.

Flurazepam has a short of duration of action of six hours or less. It is metabolized into active metabolites including N-hydroxyethylflurazepam of short duration of action, N-desalkylflurazepam of long duration of action, and the 3-hydroxy derivative of intermediate duration of action. Thus flurazepam in effect acts as a medicine of long duration of action.

Triazolam is itself a medicine with short duration of action. It is metabolized into an active metabolite α -hydroxytriazolam, which is also of short duration of action, before the final glucuronidation into an inactive metabolite. Triazolam remains as a medicine of short duration of action. The case of midazolam is similar to triazolam and it is a medicine of short duration of action.

Alprazolam is a medicine of intermediate duration of action. It has an active metabolite of shorter duration of action. Alprazolam remains as a medicine with intermediate duration of action.

Table 2. Rate of Absorption and Half Life of BDZs

| Drug | Absorption | Half life | Metabolite |
|------------------|------------|-------------|-------------|
| Alprazolam | medium | 12 hr | less active |
| Bromazepam | medium | 12 hr (>12) | |
| Chlordiazepoxide | medium | 18 hr | > 30 hr |
| Clonazepam | rapid | > 24 hr | |
| Diazepam | rapid | > 20 hr | > 100 hr |
| Flunitrazepam | rapid | 24 hr | > 24 hr |
| Flurazepam | rapid | pro-drug | > 100 hr |
| Lorazepam | medium | 15 hr | no |
| Midazolam | rapid | < 6 hr | no |
| Triazolam | rapid | < 6 hr | no |

Table 2 shows the rate of absorption and half life of some of the common benzodiazepines. Clonazepam, diazepam, flunitrazepam, flurazepam, midazolam and triazolam are regarded as medicine of rapid onset. Their duration of action varies from short duration of action to long duration of action.

Table 3. Classification of BDZs by Potency & Half Life

| | Short half life | Intermediate | Long half life |
|---------------------|----------------------------|--------------------------------------|---|
| High potency | Midazolam * Triazolam * | Alprazolam Loramet * Lorazepam | Clonazepam * Estazolam Flunitrazepam * |
| Low potency | | Bromazepam Temazepam | Chlordiazepoxide Diazepam * Flurazepam Nitrazepam Pinazepam |

* Denotes rapid onset

Table 3 shows another way of classification of the benzodiazepines by their potency and their half life. Medicines with rapid onset of action are also denoted by the asterisk. In theory for a person with difficulty to fall asleep, a medicine with rapid onset and short duration of action is desirable such that when a person wakes up from his sleep, he may no longer be under the effect of the medicine. These medicines include midazolam and triazolam. When a person has difficulty in maintaining sleep or wakes up early, a medicine with intermediate duration of action is desirable. These include alprazolam, loramet, lorazepam, bromazepam, and temazepam. For a person with difficulty to fall asleep, wakeful

sleep, short duration of sleep and anxiety in the day time, a medicine with long half life is desirable. These include diazepam, flurazepam, nitrazepam and other medicines with long half life as in the table. One needs to note that the choice of benzodiazepines for an individual patient depends also on other factors as discussed below.

When faced with a patient with insomnia, one needs to have a comprehensive assessment of the patient. These include to clarify the nature and degree of the insomnia in the patient, to understand the underlying factors contributing to the insomnia, the usual sleep pattern and sleep hygiene of the patient, the co-existing physical and psychiatric illness, treatments used by the patient, and the current degree of disturbance caused by the insomnia on the patient. Medicine is just a part of the comprehensive management of a patient with insomnia.

In general the use of benzodiazepines as sedatives for a person can shorten the onset of sleep, reduce awakenings during sleep, increase total duration of sleep, and promote a feeling of deep and refreshing sleep. One needs to ask, however, whether the sleep induced by the medicine is the same as the normal natural sleep. It is known that benzodiazepines cause suppression of slow wave sleep and suppression of rapid eye movement sleep (REM sleep). Thus while benzodiazepines do increase the duration of sleep, the sleep induced is actually light sleep. The sleep brought about by benzodiazepines is not the same as normal natural sleep.

Table 4. Side-effects of BDZs

| | | |
|----------------------------------|---|---|
| Central depressant | : | Drowsiness & sedation |
| Cerebellar | : | Inco-ordination, ataxia, dysarthria, vertigo, dizziness |
| Mood | : | Depression, irritability |
| Memory | : | ↓ Consolidation of memory |
| Psychomotor Tolerance Dependence | : | ↑ Reaction time |

Besides, there are possible side-effects of benzodiazepines in a patient. The common side-effects are listed as in Table 4. They included day time drowsiness, inco-ordination in movement, ataxia, dysarthria, vertigo, dizziness, and increase in reaction time. Thus driving or operation of machines requiring timely motor responses may become hazardous. Benzodiazepines may also lead to depression and irritability. It also leads to impairment in the consolidation of memory. Some patients may forget what they have said or done in the period after they have taken a certain dosage of a benzodiazepine sedative. With continual use of a benzodiazepine over a period of time tolerance to its effect may occur. This is called tolerance. In the majority of patients, one does not observe the tendency to increase the dosage of the medicine over time. Any tendency to increase the dosage of the benzodiazepine with time should raise caution to the development of dependence. Both physical and psychological dependence to benzodiazepines can occur.

Table 5. Different BDZ Discontinuance Syndrome

| | Type of Symptoms | Severity VS Original Symptoms | Course |
|-------------------|------------------|-------------------------------|----------------------------------|
| Rebound | Same as original | More | Rapid onset temporary |
| Recurrence | Same as original | Same | Gradual onset continue |
| Withdrawal | New symptoms | Variable | Early or late Lasts 2 – 4 wks |

It needs to be noted that not all symptoms that develop in a patient on stopping the benzodiazepine he is taking means dependence. When a patient develops symptoms after stopping the benzodiazepine, it is called benzodiazepine discontinuance syndrome. There are three situations in the benzodiazepine discontinuance syndrome. The rebound syndrome has symptoms same as the original symptoms the patient has had, and they occur rapidly and can be of even more severe intensity as a patient stops his benzodiazepine, but the symptoms last only temporarily. The recurrence syndrome has symptoms same as the original symptoms the patient has had, and they have a gradual onset and persist. The withdrawal syndrome has symptoms more than the original symptoms of the patient, and they can be started early or late and usually last for two to four weeks. Much longer duration of withdrawal syndrome has been observed. The presence of withdrawal syndrome indicates the development of physical dependence.

Table 6. BDZ Discontinuance Syndrome

| Very Frequent | Common | Uncommon |
|--|--|---|
| Anxiety Insomnia Restlessness Agitation Irritation Muscle tension | Nausea Lethargy Coryza Diaphoresis Hyperacusis Aches & pains Blurred vision Depression Hyperreflexia Ataxia | Seizures Persistent tinnitus Confusion Paranoid delusion Hallucination Psychosis |

Table 6 lists the symptoms seen in the benzodiazepine discontinuation syndrome. Anxiety, insomnia, restlessness, agitation, irritation and muscle tension are the very frequent symptoms. These are often the symptoms leading to the initiation of benzodiazepine for a patient. Common symptoms include lethargy, hyperacusis, aches, and pain, hyperreflexia and depression. Uncommon but severe symptoms can occur including seizures, confusion, delusion and hallucination.

Table 7. Risk Factors Related to BDZ Dependence

| | |
|---|---|
| <ul style="list-style-type: none"> • High dose • Duration of use • BDZ with short half life • Patient characteristics: <ul style="list-style-type: none"> – Previous dependence – Chronic illnesses – Chronic dysphoria | <ul style="list-style-type: none"> – Personality disorders – Chronic insomnia |
|---|---|

In view of the possible development of dependence in individual patients, one needs to assess the likely risk of dependence of benzodiazepine when a patient is prescribed the medicine. Table 7 lists the risk factors related to benzodiazepine dependence. High dose is regarded as likely to increase the risk of dependence. However, it is also observed that a patient on a therapeutic dose of benzodiazepine may develop withdrawal features on stopping the medicine. The longer the duration of use of the benzodiazepine the higher is the risk of dependence. It is also not certain as to what duration is too long a duration. Some may develop withdrawal syndrome after a few weeks of use while some may develop withdrawal syndrome after a few months. Development after discontinuance symptoms has been reported after as short as a week of use of a benzodiazepine. Benzodiazepines with short half-life are regarded as more likely to have stronger and quicker onset of discontinuance symptoms. Patients with previous history of alcohol dependence or substance dependence, chronic illnesses, chronic dysphoria, and borderline or dependent type of personality disorder, and chronic insomnia have higher risk of developing benzodiazepine dependence.

With the above discussion it can be seen that cautions have to be exercised when benzodiazepine is considered as a medicine for a patient with insomnia. According to the UK Committee of Safety of Medicine in 1988, benzodiazepine is indicated when the insomnia in a patient is severe and disabling, and the subject is in extreme distress. It is advised that the lowest dosage should be used and for a duration not beyond four weeks. The medicine should be gradually tapered off when withdrawn from the patient.

In psychiatric conditions benzodiazepines are also indicated in severe disabling anxiety, detoxification treatment of certain substance dependence, akathisia, and mania.

It needs to be noted that the clinical trials of the use of individual benzodiazepines are usually for durations of a few weeks to a few months. At the moment there are recommended usual or maximum duration of usage of individual benzodiazepines. Some examples are listed as in Table 8.

Table 8. Usual Duration of Use of BDZs

| Duration of Use | | Duration of Use | |
|-----------------|--------------|-----------------|-----------------------|
| Bromazepam | 8 – 12 weeks | Loramet | a few days to 4 weeks |
| Clorazepate | 4 – 12 weeks | Lorazepam | 2 – 4 weeks |
| Diazepam | 2 – 3 months | Midazolam | 2 weeks |
| Flunitrazepam | 4 weeks | Triazolam | 7 – 10 days |

Table 9. Caution in the use of BDZs

| |
|---|
| <ul style="list-style-type: none"> • The elderly • Those with impaired liver function • Those with pregnancy • The lactating mother • Those with acute glaucoma • Those with myasthenia gravis • Paradoxical reactions – Anxiety, insomnia, restlessness, agitation, irritability, aggressiveness, confusion |
|---|

There are situations in which special caution has to be taken when a benzodiazepine is prescribed as in Table 9. For the elderly and those with impaired liver function the dose may have to be reduced. The likely side-effects of inco-ordination and paradoxical reaction with the use of benzodiazepines in the elderly have to be noted. Paradoxical reaction is a condition after taking benzodiazepine in some patients with features instead of the expected sedation but of anxiety, insomnia, restlessness, agitation, irritability, aggressiveness, and confusion.

Table 10. Interactions of BDZs with Other Drugs

| | | | |
|-------------------------|-----------------------------|--|-------------------------|
| ↓ Absorption | : Antacids | | |
| ↑ CNS depression | : Antihistamines Ethanol | Barbiturates Cyclic antidepressants | |
| ↑ BDZ levels | : Cimetidine Disulfiram | Erythromycin Estrogens | Fluoxetine Isoniazid |
| ↓ Benzodiazepine levels | : Carbamazepine | | |

Benzodiazepines may have interactions with other drugs when concomitantly administered to the patient. The common interactions are listed in Table 10. The absorption of benzodiazepines may be reduced by the simultaneous administration of antacids. The central depressant effect of benzodiazepines may be accentuated with the concomitant use of other medicine including anti-histamines, alcohol and cyclic anti-depressants. The blood level of benzodiazepines may be increased with the simultaneous administration of cimetidine, erythromycin, fluoxetine, and estrogens. The blood level of benzodiazepines is reduced by the simultaneous use of carbamazepine.

It should be noted that absorption of diazepam with the intramuscular administration is erratic and it is slower than the absorption with the oral route of administration.

There are contra-indications to the use of benzodiazepine. These include sleep apnoea, severe respiratory insufficiency and known hypersensitivity.

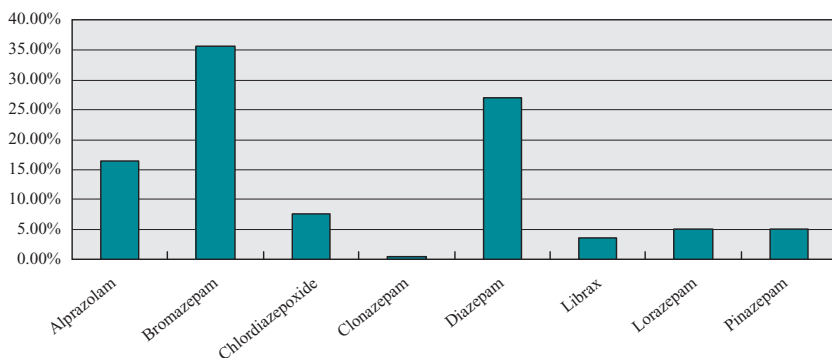
In general pharmaceutical companies should have updated information covering the use and caution of their benzodiazepine products, ensuring the accuracy of the updated information is within the domain of governance of the authorities concerned. It is recommended that a medical practitioner could keep up with the updated information from the pharmaceutical companies when benzodiazepine products are purchased from the companies in addition to the clinical pharmacology information of the benzodiazepines from updated standard texts and journal articles.

A Survey of the Use of Benzodiazepines in Outpatient Clinics in Hong Kong

A small survey was done towards the end of 2002. The outpatient clinic of two private hospitals and a general outpatient clinic of a public hospital were invited to supply information from about one hundred consecutive prescriptions that include benzodiazepines. The information included the age and sex of the patient, the name and the dosage of the benzodiazepine prescribed.

The sample includes 342 subjects with the mean age of 50 and an age range from 19 to 93. The male to female sex ratio is about 1 to 2. This indicates a higher proportion of female is seen in the patient sample as compared to the general population. In about 6% of the subjects two different kinds of benzodiazepines were prescribed, and in 0.6% three different kinds of benzodiazepines were prescribed.

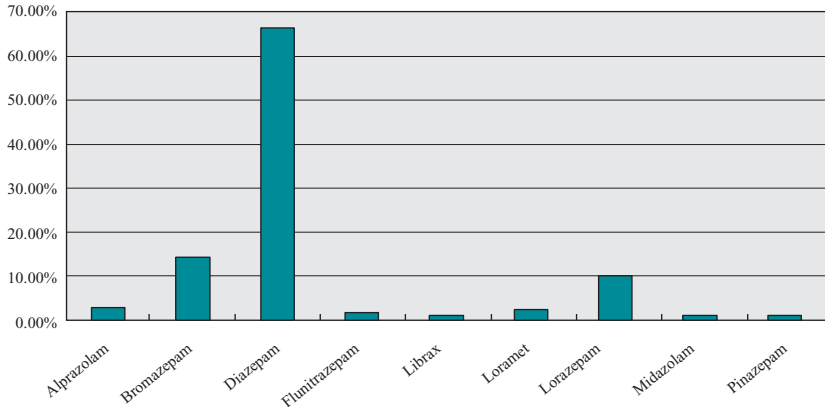
Figure 3. Frequency Distribution of Benzodiazepines Prescribed to 196 Outpatients for Day Time Use (Age Range: 19-83, Mean 48.7; M:F = 1:3)



For 196 subjects the benzodiazepines were prescribed for daytime use and the frequency distribution of the benzodiazepines prescribed is shown in Figure 3. The mean age of these subjects is 48.7 with a range from 19 to 83, and the male to female sex ratio is 1 to 3. This

indicates that a significantly higher proportion of female is represented in patients who are prescribed benzodiazepines in daytime use. Bromazepam, diazepam and alprazolam are the more commonly used benzodiazepines in this sample of subjects. The dosage range of the individual benzodiazepines prescribed is within the usual recommended range. One of the subjects, however, is prescribed simultaneously alprazolam 0.25 mg three times a day and diazepam 2 mg three times a day.

Figure 4. Frequency Distribution of Benzodiazepines Prescribed in 169 Outpatients for Use Before Sleep (Age Range: 19-93, Mean 51, > 60 = 26.7%; M:F = 2:3)



For 169 subjects the benzodiazepines were prescribed for night time use and the frequency distribution of the benzodiazepines prescribed is shown in Figure 4. The mean age of these subjects is 51 with a range from 19 to 93, and the male to female sex ration is 2 to 3. This indicates that while female has a higher representation in the patient sample, relatively more male subjects are seen in those requiring medicine before sleep. It is also observed that 27% of the subjects are above 60 of age. This indicates that the elderly may be more likely to suffer from insomnia and/or other psychiatric disorder requiring medicine for sleep. As discussed above, caution has to be exercised when the benzodiazepine is prescribed for the elderly. Diazepam, bromazepam and lorazepam are the more commonly used benzodiazepines in this sample of subjects. The dosage range of the individual benzodiazepines prescribed is within the usual recommended range.

This survey has a number of limitations and the information has not allowed a comprehensive evaluation of the use of benzodiazepines. The survey has not covered the indications of the benzodiazepines in individual subjects, the psychiatric and physical conditions of the subjects, the concomitant medications, psychosocial treatments provided, the duration of benzodiazepines already used in the subjects, the subjective and objective usefulness of the benzodiazepines, the frequency of side-effects, the frequency of discontinuance symptoms and the frequency of benzodiazepine dependence in the clinical population, if any.

Abuse of Benzodiazepines in Hong Kong

Abuse of benzodiazepines in Hong Kong has been reported in the Central Registry of Drug Abusers (CRDA) for more than a decade. The number of persons abusing benzodiazepines reported in the CRDA in the past decade is shown in Figure 5. The number of abusers for the year 2002 only represents findings in the first half of the year. Different trends are seen for the three different benzodiazepines shown. The number of person abusing flunitrazepam has its peak in 1994 and then its gradual decline to a low number by 1998. Flunitrazepam remains as a drug used by the abusers. Triazolam and midazolam are grouped together in the CRDA data. The number of persons abusing these two medicine rose to a high level by 1997 when the number was almost doubled compared with that of the peak of flunitrazepam. The numbers of abusers using triazolam and midazolam remain at a high level in the subsequent years. The final number of abusers for the year 2002 is likely to remain at about the same high level. Diazepam has returned into the drugs of abuse by abusers from 1997 and rising year by year. The final number of diazepam abusers is likely to be as much as for the year 2000.

Figure 5. Number of Reported Persons Abusing BDZ in HK

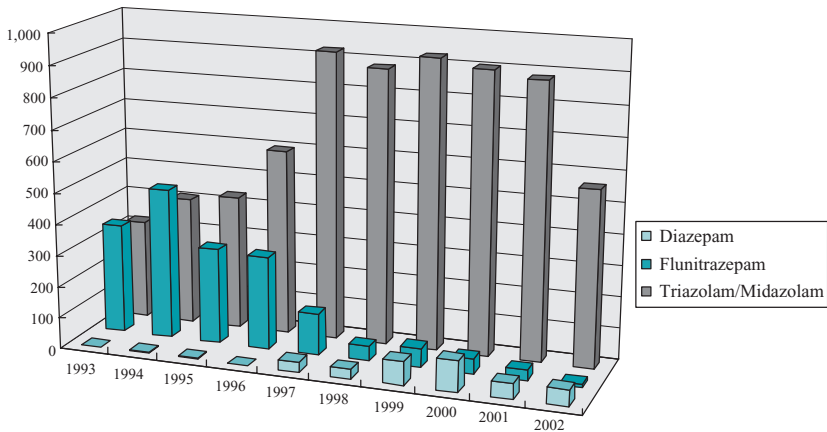


Figure 6. Number of Reported Persons Abusing Flunitrazepam in HK (CRDA)

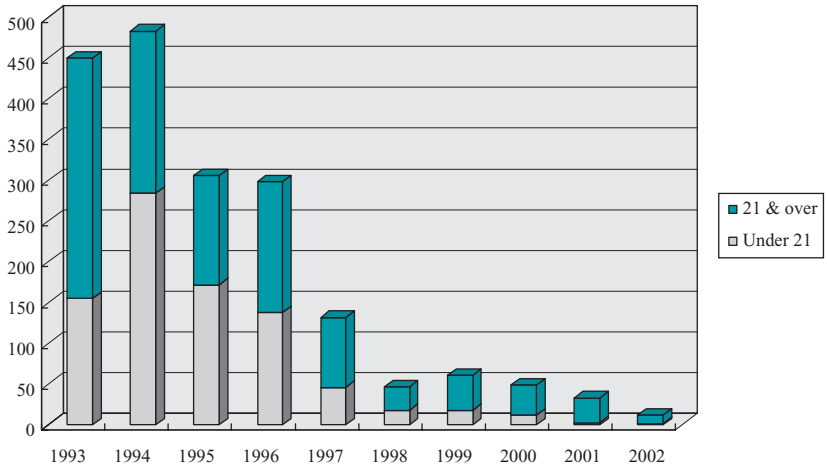


Figure 7. Number of Reported Persons Abusing Trizolam/Midazolam in HK (CRDA)

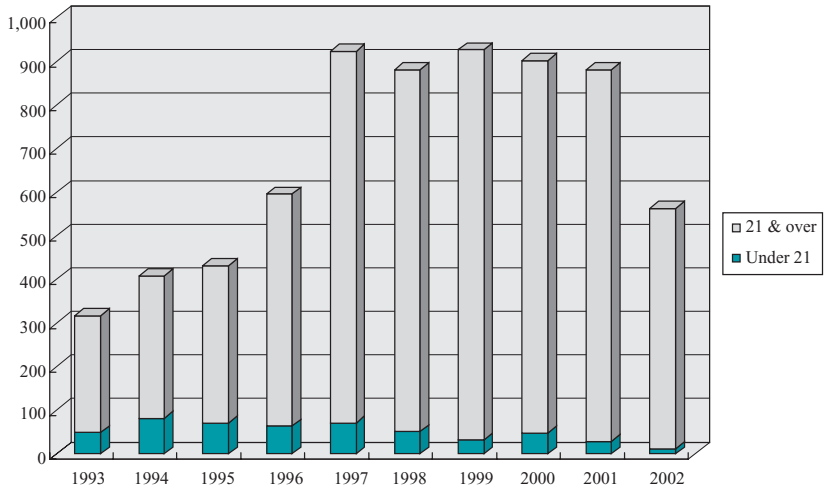
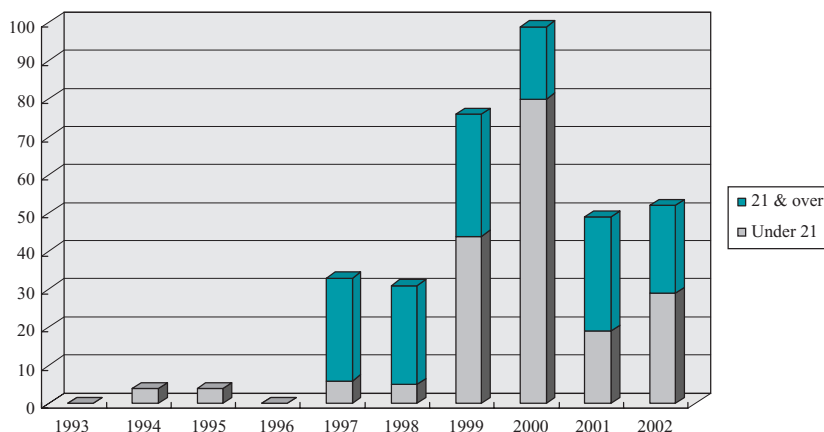


Figure 8. Number of Reported Persons Abusing Diazepam in HK (CRDA)



Figures 6, 7 and 8 show the number of person abusing the benzodiazepines according to those under 21 of age and those 21 of age and above. Figure 6 shows that those under 21 of age have constituted a significant proportion of the flunitrazepam abusers reported in the period from 1993 to 1996. From 1997 onwards those under 21 of age have decreased year by year while the total numbers of flunitrazepam abusers also decrease over the years. For triazolam and midazolam the situation is different. As shown in Figure 7, those of 21 of age and above remain as the major abusers of the two medicines. As for diazepam, Figure 8 shows that those under 21 of age have returned to take diazepam as a drug of abuse, and the trend has yet to be seen to decrease.

While flunitrazepam, triazolam, and midazolam are not among the most commonly used benzodiazepines in the current survey reported, it remains a caution for medical practitioners as to the possibility of abuse when such medicine is prescribed to a patient. Diazepam is among the most commonly prescribed medicine and it has also become an abused drug of choice among those under 21. Medical practitioners have to be extra careful when the medicine is requested from a young patient.

Another source of information of psychotropic substance abuse has been obtained from PS 33, a psychoactive substance counseling centre run by the Hong Kong Christian Service. There are 86 psychotropic substance abusers reported in the recent two years. The majority of the abusers are in the age range of 21 to 40. The male to female sex ratio is about 1 to 1. The more commonly abused psychotropic substances among these abusers are zopiclone, estazolam and erimin. Zopiclone is a commonly prescribed non-benzodiazepine medicine in Hong Kong. Both estazolam and erimin are not registered medicine in Hong Kong. They can be purchased from countries nearby to Hong Kong.

From the information of abusers observed in CRDA and the information of abusers seen in PS 33, the more commonly abused benzodiazepines are not those benzodiazepine commonly

prescribed by medical practitioners other than diazepam. Flunitrazepam, triazolam, and midazolam are among the commonly abused substances and they are prescribed in clinical practice. They belong to the benzodiazepines with high potency and rapid onset of action. Furthermore zopiclone, a non-benzodiazepine medicine, is a commonly abused medicine and probably also commonly prescribed by medical practitioners. The age and sex distribution of the clinical population prescribed benzodiazepines are different from the age and sex distribution of the abusers. The information has not shown the major sources of the abused psychotropic substances and where the majority of the subjects may have turned to for treatments.

Use and Misuse of Benzodiazepines

From the above information, we need to learn more about the use and usefulness of benzodiazepines for patients in Hong Kong. The frequency of discontinuance symptoms from and dependence on benzodiazepines and the local associated dosage need further research. While the doctor should be cautious when the doctor prescribes a benzodiazepine to a patient, a patient should receive the appropriate treatment including the appropriate use of benzodiazepine when the condition of the patient warrants the use of the benzodiazepine as part of the management. With the current inclusion of benzodiazepines under the Dangerous Drug Ordinance and the promulgation of guidelines for the use of dangerous drugs by the Hong Kong Medical Council, to what degree benzodiazepines have been prescribed more appropriately and to what degree patients may not have received benzodiazepine appropriately await to be answered. Benzodiazepines in addition to non-benzodiazepines remain as a likely choice of substance of abuse. Doctors are in a good position for education of the public, early detection of abusers, institution of appropriate treatments and arrangement of abusers to specialized substance abuse counseling centres and clinics.

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The Use and Abuse of Non-benzodiazepine Sedatives

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Sedatives and hypnotics, especially the benzodiazepines, are widely used in medical practice in the treatment of anxiety, insomnia, epilepsy, and for several other indications. Clinical practitioners have attended the risks and benefits of the benzodiazepines in the treatment of anxiety and addiction medicine. The National Comorbidity Survey (USA) in 1994 found that 17.2% of the population reported an anxiety disorder in the past 12 months and 24.9% reported a lifetime history of an anxiety disorder, which established that the anxiety disorders are the most prevalent mental disorders. While the benzodiazepines were introduced as comparatively problem free compared to the barbiturates they replaced, their popularity reached unprecedented levels in the early 1970s and a backlash during the 1980s which caused a drop in its use in USA, even though there was a rise in the prevalence of the anxiety disorders for which they are used.

The Guidelines on the proper prescription and dispensing of dangerous drugs by registered practitioners (1996, The Medical Council of Hong Kong), which includes practice directions for the use of benzodiazepines (Section E1), intends to assist individual doctors in acquainting themselves along with good professional practices in providing proper treatment to their patients. It is spelled out clearly in the Newsletter of the Association (March 1996) that it is a necessary step in the attempt to curb the illegal drug sale of benzodiazepines by some black sheep in the profession. Examination of the Central Registry of Drug Abuse (50th Report) revealed little change of the percentage of individuals with the 4 most frequently abused benzodiazepines (diazepam, flunitrazepam and triazolam/midazolam) in the year 1997, 1998, 1999, 2000, 2001, and 2002 (1st half), i.e. 6.9%, 6.1%, 7.1%, 6.4%, 5.9% and 6.2%. However, available statistics of the total prescription of benzodiazepines by clinical practitioners dropped significantly since the stipulated use of the Guidelines, which spells out clearly of no intention of any restriction on proper use. Regulatory approaches as the Guidelines obviously limit the use of benzodiazepines in medical practice. There is a danger that clinicians will revert to the older and generally more toxic sedatives and hypnotics, which, in the era of benzodiazepines, have become unfamiliar. Newer sedative hypnotics like Zolpidem and Zopiclone, while enjoying their status as non-dangerous drugs in Hong Kong, are often prescribed loosely by clinicians not taking note that there is little evidence of clinical advantage in terms of their potential to induce tolerance, withdrawal, dependence, and fatal toxicity.

Use and abuse form a rather uncertain continuum. A useful working definition of abuse/misuse is any taking of a drug which harms or threatens to harm the physical or mental health or social well-being of an individual, of other individuals, or of society at large, or which is illegal (The Royal College of Psychiatrists). The following is an account of non-benzodiazepine sedating agents used and abused. They are conveniently grouped as:

- A. Prescribed drugs (including OTC drugs or health products)
 - 1. Drugs not recommended for use as sedative hypnotics
 - 2. Drugs with sedating effects but should not be used as sedative hypnotics
 - 3. Drugs used as hypnotics
 - 4. Drugs used as anxiolytic agents
- B. Recreational drugs with sedating effect
- C. Illicit drugs with sedatives as additives/adulterants
- A. **1. Drugs Not Recommended for Use as Sedative Hypnotics:**

| Drug | Use in the Past | Adverse Effects |
|--|----------------------|--|
| Barbiturates – secobarbital, pentobarbital (short-acting) | Hypnotic | Disinhibition; tolerance; intoxication; amnesia; suicide/parasuicide; fatal overdose; withdrawal; dependence |
| Non-barbiturate sedatives – methaqualone, meprobamate, glutethimide | Sedative, hypnotic | Risk of addiction; high lipid solubility makes it difficult to remove the drug by dialysis in overdose |
| Lytic cocktail (mixture of pethidine, promethazine, chlorpromazine) IM injection | Sedation & analgesia | High rate of therapeutic failure (29%) and incidence of life threatening adverse events (4%) |

Barbiturates reversibly suppress the activity of all excitable tissue, with the central nervous system being particularly sensitive to these effects. Notable during medical use of the barbiturates for both sedation and hypnosis is the rapid development of tolerance, with a common tendency to raise the dose on chronic administration. Barbiturates also affect the GABA system, producing both a cross-tolerance to other sedating drugs, including alcohol and the benzodiazepines, and a heightened risk of fatal overdose reactions. Short acting barbiturates (e.g. secobarbital, pentobarbital) are primary drugs of abuse. Intoxication is similar to intoxication with alcohol, producing a state of disinhibition, in which mood is elevated; self criticism, anxiety, and guilt are reduced; and energy and self confidence are increased.

Non-barbiturate sedatives like methaqualone, meprobamate and glutethimide were developed to replace barbiturates but failed. They are not recommended because of their addictive potential and the severity of withdrawal, as well as because the treatment of overdoses from these drugs is particularly hazardous. Methaqualone is still being abused in the locality because of its dissociative “high” and reputed aphrodisiac properties.

Lytic cocktail had been commonly used by paediatricians to sedate children for painful or non-painful procedures. It is not recommended for use because of the possible risk of life-threatening adverse events and high rate of therapeutic failure.

A. 2. Drugs with Sedating Effects but Should Not Be Used as Sedatives:

| Drug | Use | Adverse effects |
|--|--|---|
| Antipsychotic drugs e.g. chlorpromazine (Largactil), thioridazine (melleril), clozapine (clozaril), flupentixol (deanxit, with melitracen) | Anti-psychotic | Akathesia; acute dyskinesia; extrapyramidal side effects; Parkinsonism; dystonia, tardive dyskinesia; agranulocytosis, seizure, hyperpr olatinemia, cardiovascular effects |
| Tricyclic antidepressant e.g. Amitriptyline | Depression | Overdose & toxicity; anticholinergic side effects; delirium |
| Paraldehyde | Anti-convulsant (fallen out of favour) | Its use as sedative and hypnotic (IM, rectal) also out of favour due to bad odour, long duration of action, painful IMI & risk of abscess formation. |
| Pethidine | Analgesic | Causes sedation, respiratory depression and G.I. immobility |
| Phenobarbital & amobarbital | Anti-epileptic | Can alleviate anxiety if dose and duration of use limited. Risk of withdrawal including fits makes it not a sedative of choice. |
| Ketamine | Induction agent for general anesthesia | <ul style="list-style-type: none"> • A derivative of PCP (phencyclidine), a sedating agent for short diagnostic and therapeutic procedure, an analgesic for painful procedures. • “Dissociative anesthesia” • “Emergence reaction” |
| Dextromethorphan (Romilar) | Cough suppressant | When taken in high doses can produce effects similar to PCP and ketamine – distorts perception of sight and sound, feeling of detachment (dissociation) from environment and self. |

The majority of **antipsychotic drugs** and **tricyclic antidepressants** produce some degree of sedation or drowsiness. With tricyclic antidepressants, drowsiness appears to parallel their antihistaminic activity and may also correlate with their anticholinergic potency. Amitriptyline and trazodone are most sedating. Among the antipsychotic drugs, clozapine, chlorpromazine, and thioridazine are most sedating. Anticholinergic effects are manifested peripherally by dry mouth, blurred vision, tachycardia, increased or decreased sweating, constipation, and urinary retention. CNS manifestations include confusion, stuttering speech, disorientation, delirium, and hallucination. And there are idiosyncratic drug reactions which include agranulocytosis, myocardial depression and postural hypotensive effects, lowering of seizure threshold etc, all preclude their use as safe sedating and hypnotic agents. And there is also the risk of tardive dyskinesia which clinician should attend to. Small doses cautiously utilized for brief periods of time is the rule.

Paraldehyde has fallen out of favour even as an anticonvulsant. It was seldom mentioned among the list of drugs for sedation in recent textbooks and journal articles, due to its bad odour, long duration of action, the painful intramuscular injections and risk of abscess formation. Administration through the rectal route is an option since it is equally effective and does not cause pain. It is contraindicated in patients with poor pulmonary or hepatic function. In overdosage, it can cause lethal respiratory depression and hypotension.

Phenobarbital, a long acting barbiturate, is used in the management of epilepsy. Abuse of the drug is relatively uncommon. However, if used as anxiolytic agent, the dose and duration of use should be limited. The risk of withdrawal including fits must be borne in mind.

Both **petidine**, an analgesic; and **ketamine**, an agent for induction of general anesthesia, are primary drug of abuse. Although both produce sedation, they should not be used as sedative or hypnotic. **Dextromethorphan**, a cough suppressant, when taken in high doses can produce effects similar to phencyclidine (PCP) and ketamine – sedation, distorted perception of sight and sound, dissociation from self and environment. It is occasionally abused by young people in the locality. It should not be used as sedative at all.

A. 3. Drugs Used as Hypnotics:

| Drug | Use | Action | Remarks |
|-----------------|--------------------|---|---|
| Chloral Hydrate | Effective hypnotic | <ul style="list-style-type: none"> • Rapid onset, 30 min • Duration 6-8 hours • 0.5-2gm dose | <ul style="list-style-type: none"> • G.I. irritation. • Can lead to transient increase levels of Warfarin & risk of haemorrhage in patients on anticoagulant. |

| Drug | Use | Action | Remarks |
|---------------------|--|--|--|
| Zolpidem (Stilnox) | Hypnotic (resembles Triazolam) | <ul style="list-style-type: none"> • Dose 10mg with subsequent reduction to 5mg at bed time • Rapid onset • Half life 1.5-4.5 hours | <ul style="list-style-type: none"> • Imidazopyridine. Not a BZD but binds selectively to a subset of BZD receptors. • Impairs short & long-term memory, psychomotor performance, postural sway. • Rapidly causes tolerance, confusion, memory & behaviour disturbance & psychotic reaction. • S.E. includes drowsiness, dizziness, headache, G.I. upset. • Abuse potential less than BZD, as reported less enjoyable. • Safe in overdose; reversed by BZD antagonist Flumazenil. |
| Zopiclone (Imovane) | Hypnotic | <ul style="list-style-type: none"> • 7.5mg is the optimum dose • Rapid onset • Half-life 4 hours • No hangover effect | <ul style="list-style-type: none"> • Chemically unrelated to Zolpidem & BZD, but similar pharmacological actions – sedative, hypnotic, anticonvulsant, muscle relaxant & anti-aggressive. • Little evidence it offers any advantage in terms of its potential to induce tolerance, withdrawal or dependence. • Fatalities following overdose reported, which is managed with Flumazenil. |
| Melatonin | Hypnotic (induces sleep) available as health product | <ul style="list-style-type: none"> • Dose 1 to 5mg (optimal dose not determined) | <ul style="list-style-type: none"> • Pineal gland manufactures & releases serotonin, which is catalysed in vivo to melatonin – a natural endogenous regulator of sleep & light-dark accommodation. • Safe & minimal S.E. (over-sedation). No potential for physical dependency or addiction. |
| Chlor-methiazole | Sedative Hypnotic | <ul style="list-style-type: none"> • Rapid onset & action, short half life • 250-500mg at bed time | <ul style="list-style-type: none"> • A thiamine derivative. • Anti-convulsant property, can be used in alcohol withdrawal. • Indicated for use as hypnotic only in the elderly though they may be more sensitive to it. • Dependence & abuse reported. • Caution in cardiac, pulmonary disease & hepatic impairment. |

It is estimated that a third of the population has sleep problems. As a result, hypnotics (sleeping pills) are among the most frequently prescribed of all drugs. Such reliance on sleeping pills is probably unwise. Hypnotic induced sleep is abnormal and may not be as valuable as natural sleep. Hypnotics provide symptomatic relief of insomnia. Before a clinician prescribes hypnotics, diagnosis should be made: to rule out transient insomnia which may be result of disturbance influence as grief, anxiety, noise, or stimulation and a change in schedule in which a person shifts sleep hours or travels rapidly to another time zone; to diagnose on the cause of chronic insomnia which is often a symptom of psychiatric disorders requiring proper psychiatric treatment rather than a prescription of hypnotics, or underlying drug dependence, nocturnal myoclonus, sleep apnoea. Clinicians should pay attention to non-pharmacologic interventions and take note that sleep is powerfully influenced by suggestion, i.e. placebos influence sleep parameters in sleep studies.

Chloral hydrate, the oldest of hypnotics, produces a decrease in sleep latency, and in therapeutic doses, little effect on respiration or blood pressure. Toxic doses, however, produce severe respiratory depression and hypotension. It has an unpleasant taste and is irritating to the skin and mucous membranes, and also gastric irritation especially when taken on an empty stomach.

Chlormethiazole, which is indicated for use as hypnotic in elderly though they may be more sensitive to it, and requires caution in patients with cardiac, hepatic and pulmonary diseases. Both should not be viewed advantageous over benzodiazepine hypnotics at all.

In recent years a variety of alternatives to the benzodiazepines have been available to treat insomnia. **Zolpidem** (Stilnox) is a rapid onset, short duration of action imidazopyridine that acts on the benzodiazepine receptor of the GABA system. It and Zopiclone, as both are not classified as dangerous drug in the locality, have largely replaced the benzodiazepines as hypnotic agents. It lacks the anxiolytic, anticonvulsant, and muscle relaxant properties of the benzodiazepines. Its sedative effects are additive with alcohol. Like triazolam, it is reinforcing to alcoholics and drug addicts and it impairs memory and performance of complex tasks. Chronic abuse has been reported with tolerance, induced psychotic reactions, and acute overdose. There is little evidence that it offers any advantage over short-acting benzodiazepines in terms of residual effects the next day, or its potential to induce tolerance or withdrawal symptoms or dependence.

Zopiclone (Imovane), a cyclopyrrolone, differs chemically from benzodiazepines and barbiturates but has the same pharmacologic actions – a sedative-hypnotic profile together with anticonvulsant, muscle relaxant and anti-aggressive properties. It binds with benzodiazepine receptors in the central nervous system. Absorption is rapid after oral administration and elimination half-life is short (4 hours). There is rebound responses with discontinuation of Zopiclone after only 14 days. A large survey in France revealed adverse events including bitter taste, dry mouth, difficulty arising in the morning, sleepiness, nausea, and nightmares. Other reports include potentially serious reactions including hallucinations,

amnesia, and behavioural disturbances. Fatalities following overdose have been increasingly reported overseas and locally. It is contraindicated in patients with severe hepatic disease. There is little evidence of its advantage compared to benzodiazepines in terms of potential of inducing tolerance, withdrawal and dependence. As benzodiazepines, it should be reserved for patients with severe sleep disturbance and its duration of use limited to 28 days; care should be taken in elderly, those with history of previous psychiatric illness, or who are prone to drug abuse.

Melatonin may be helpful in the alleviation of jet lag and improving accommodation to schedule changes in shift work. It appears to be a natural endogenous regulator of sleep and light-dark accommodation. However, optimal dose and timing of administration need to be established. A study of random samples of over-the-counter melatonin revealed unknown contaminants presumably introduced during the manufacturing process. Studies examining both efficacy and safety are lacking. It is currently available as a nutritional product in health food stores.

A. 4. Drugs Used as Anxiolytic Agents:

| Drug | Use | Action | Remarks |
|--|------------|---|---|
| Buspirone (Buspar) | Anxiolytic | <ul style="list-style-type: none"> • Dose 5mg t.i.d. for first week, gradual daily dose increments of 2.5mg to 5mg every 2-4 days (15-30mg per day) • Take at least one week to onset of effect • Cannot be used on p.r.n. basis | <ul style="list-style-type: none"> • Selective 5-HT_{1A} agonist antagonist. • Non sedating. Not interfere with motor co-ordination or complex task performance. • Not induce sleep. • No tolerance, withdrawal & dependence. • Difficult to transition a patient from BZD to it. |
| Beta-blockers (propranolol, metoprolol, atenolol) | Anxiolytic | <ul style="list-style-type: none"> • Inderal 10-20mg 3-4 times daily | <ul style="list-style-type: none"> • Indicated for patients with severe persistent anxiety having physiological components of tachycardia, tremor, sweating. • Adverse effects: <ol style="list-style-type: none"> 1. Worsen depression, esp in high dose 2. Produce toxic organic brain syndrome in sensitive individual 3. Physical contraindication e.g. asthma, CHF, poor myocardial function |

| Drug | Use | Action | Remarks |
|---|--------------------------|---|--|
| Anti-histamine – Diphenhydramine (Benadryl), Hydroxyzine (Atarax) | Mild sedative & hypnotic | <ul style="list-style-type: none"> Benadryl or Atarax 25 to 100mg at bed time as hypnotic, 10-25mg t.i.d. as mild sedative | <ul style="list-style-type: none"> Non-addicting is its advantage. It's anticholinergic effect may be troublesome in elderly patient or organic dysfunction. |

Despite the lengthy history of the use of barbiturates, and the extensive experience with benzodiazepines and a variety of other sedative medications, the mechanisms of action of these agents are not fully understood. Many sedatives used for the relief of anxiety and the induction of sleep exert a general CNS depressant effect, which is dose related. Benzodiazepines are not perfect, having associated problems of abuse, withdrawal, dependence, cognitive impairment, and interactions with other CNS depressants. A number of non-benzodiazepine anxiety reducing agents are currently under evaluation. Even though these agents are technically not CNS depressants, they are discussed briefly here because they are used in clinical conditions historically reserved for benzodiazepines.

Buspirone (Buspar) is the best known and most thoroughly studied of these agents. It is structurally unlike that of any other sedatives. It does not produce significant sedative action or hypnotic effect, yet it alleviates many symptoms of general anxiety. Its anxiolytic effects take from days to weeks to develop. It does not cross-react with benzodiazepines, and will not protect against benzodiazepine withdrawal symptoms, nor does it produce tolerance or dependency of its own. It does not possess anti-convulsant or muscle relaxing properties. Its anxiolytic effects are less dramatic from the patients' point of view than similar effects produced by benzodiazepines. Clinical observations suggest that patients with a history of benzodiazepines abuse are resistant to the anxiolytic effects of buspirone.

Many patients with severe persistent anxiety have a physiological component with associated tachycardia, palpitations, tremor, and sweating, which are secondary to sympathetic nervous system hyperactivity. Blockade of beta-adrenergic receptors by drugs such as propranolol, metoprolol, and atenolol will produce a slowing of heart rate, decrease in palpitations, and a reduction in anxiety associated sweating and tremor. **Beta-receptor antagonists** are not CNS depressants, do not produce drug dependency, and are not generally associated with the development of drowsiness, which may occur with conventional sedative agents. It is known that propranolol with dosage in excess of the usual dosage employed in the management of anxiety may produce or worsen depression. In sensitive individuals, it can produce a toxic organic brain syndrome which is not dose related.

Sedating **antihistamines** have been used for many years in anxiety and insomnia. These drugs have the advantage of being not addictive. However, they exert some anticholinergic effect, which may be mildly apparent or may become troublesome, particularly in the elderly and patient with organic dysfunction. Control studies indicate that OTC sleep aids and sedatives are probably little more effective than placebo or aspirin, and they are significantly less effective than the benzodiazepines, and they had increased rates of side effects, including daytime sleepiness and dizziness.

B. Recreational Drugs with Sedating Effects:

1. Opiates

Morphine, derives its name from Morpheus, the gods of dreams. Heroin addicts talk of “being on the nod” to describe its acute effects. However, single doses of heroin, morphine, and methadone are stimulating and suppress the REM sleep.

2. Alcohol and cannabis

Both alcohol and cannabis could be classified pharmacologically as sedative hypnotics. Alcohol is the oldest known sedative used both medically and non-medically. Small doses of alcohol, in both alcoholics and non-drinkers, reduce latency to sleep and amount of REM sleep. It increases total sleep time. But moderate drinking before bedtime is typically followed by strong sympathetic nervous system activity that interrupts sleep and some people could be awakened from intense dreaming with sweating and headache. Chronic drinking causes sleep abnormalities that often last for months after sobriety is achieved.

Cannabis is among the most widely abused of the drugs known. THC is the most active ingredient whose effects include alteration of mood, toxic reaction and a variety of mental and physiological damages to young abusers which arouse public anxiety. For users, the first night of cannabis use is accompanied by an increase in deep sleep and reduction in REM sleep. With chronic use, levels return to normal. The effects of THC on the CNS are similar to those of alcohol and it appears that they potentiate each other. The toxic effects of THC with impairment of ability to estimate time and distance and other motor performance significantly decreases automobile driving ability for up to 8 hours after use.

3. Nicotine

Nicotine is responsible for the majority of the pharmacologic effects of tobacco consumption. Nicotine administration to humans exerts an alerting effect, and can facilitate memory and attention, while producing a mild relaxant action. Modest doses may decrease irritability. However, discontinuation is followed by a mild withdrawal syndrome including irritability, anxiety, restlessness, difficulty to concentrate, etc. It should not be used as an anxiolytic and is bad for sleep.

4. **GHB (Gamma-hydroxybutyric acid)**

Abused for its sedative, anabolic and euphorogenic properties, it has been used medically as an anesthetic and also in treating alcohol withdrawal. It is usually abused in liquid drink with varying strength and incorrect dosing often lead to overdosing – potentially fatal respiratory depression, seizure (especially when accompanied with use of methamphetamine), vomiting and discoordination. Adverse effects increase with alcohol and MDMA. Tolerance, withdrawal (insomnia, muscle cramp, tremor, anxiety) and dependence occur. It is often mistaken as a safe, natural (as it is present in the body in small amount), and non-addictive hypnotic or anabolic. It is available in shops as ingredient in health food. It's popularly used as date-rape drug.

D. Illicit Drugs with Sedatives as Additives or Adulterants:

1. **Heroin**

Concomitant use of other drugs (polydrug use or unknowingly as adulterants in street heroin), particularly central nervous system depressants such as benzodiazepines and barbiturates appears to be a common practice among heroin users. This can substantially increase the likelihood of a fatal outcome following injection of heroin, due to the potentiation of the respiratory depressant effects of heroin. In the presence of other CNS depressant drugs a normal or usual dose of heroin may prove fatal. Additives of barbiturates and benzodiazepines adds difficulty to the attempts of withdrawal from heroin even with the use of substitution drugs like methadone. Withdrawal fits are frequently reported during detoxification when the withdrawal from barbiturates and/or benzodiazepines are not taken care of. The Hong Kong Government Laboratory has recently reported the presence of the following sedating adulterants in seized street heroin: phenobarbital, midazolam, estazolam.

2. **Ecstasy**

One of the most popular recreational drugs in Hong Kong is Ecstasy, which refers to the designer drug named MDMA (methylene-dioxy-methamphetamine), a hallucinogenic stimulant. Ecstasy tablet may contain pure MDMA but usually with a variety of additives/adulterants which contribute to unknown types of drug interactions. Sedative hypnotics are frequently found. The Hong Kong Government Laboratory has recently reported the following sedating adulterants in seized Ecstasy tablets: benzodiazepines like diazepam, estazolam, midazolam; antipsychotic like chlorpromazine, clozapine; barbiturates like amobarbital, phenobarbital, barbital.